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The Ophthalmologic Manifestations of Wilson's Disease

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Fifty-three patients with Wilson's disease were studied with regard to ophthalmologic abnormalities. Of the 35 symptomatic patients initially seen and treated at the Mayo Clinic, 34 (97%) had Kayser-Fleischer rings and 6 (17%) had sunflower cataracts at the time of diagnosis. In patients followed for a year or more, penicillamine therapy resulted in improvement of the Kayser-Fleischer rings in 18 of 20 (90%) patients and total clearing of the sunflower cataracts in 4 of 5 patients. The specific pattern of copper deposition in Kayser-Fleischer rings and the improvement with treatment occurred along four reproducible stages. None of five asymptomatic siblings of patients with known Wilson's disease had Kayser-Fleischer rings at the time of initial study. In one (untreated) of the five, Kayser-Fleischer rings developed 20 months after the initial normal slit-lamp examination. The presence of Kayser-Fleischer rings, and the absence of other ophthalmologic signs (such as nystagmus, cranial nerve palsies, and other movement disorders), can be of great assistance in the diagnosis of Wilson's disease. Once the condition has been diagnosed, specific medical therapy with penicillamine and low-copper diet dramatically improves what would otherwise be an inevitably fatal course.

Wilson's disease (hepatolenticular degeneration) is an uncommon inborn error of copper metabolism inherited as an autosomal-recessive trait. Deposition of copper is widespread throughout the body, but pathologic and clinical manifestations are most prominent in the liver, brain, corneas, kidneys, and joints.

The neurologic and pathologic manifestations were first clearly described by Wilson in his classic monograph in 1912.[1] At that time, the associated ophthalmologic finding of pigmented corneal rings was unknown. The corneal rings were first described by Kayser in 1902[2] in a patient thought to have multiple sclerosis and later reported in association with hepatic cirrhosis and pseudosclerosis by Fleischer in 1909[3] and 1912.[4] A detailed account of the subsequent history of the Kayser-Fleischer ring was presented by Bothman and Rolf[5] in 1936. The presence of corneal rings is now recognized as the most common ophthalmologic finding in Wilson's disease and is an important clinical aid in diagnosis.

The term Kayser-Fleischer ring refers to a golden-brown, brownish-green, greenish-yellow, golden-yellow, bronze, or tannish-green discoloration in the zone of Descemet's membrane in the limbic region of the cornea (Fig. 1). It often can be detected with the unaided eye

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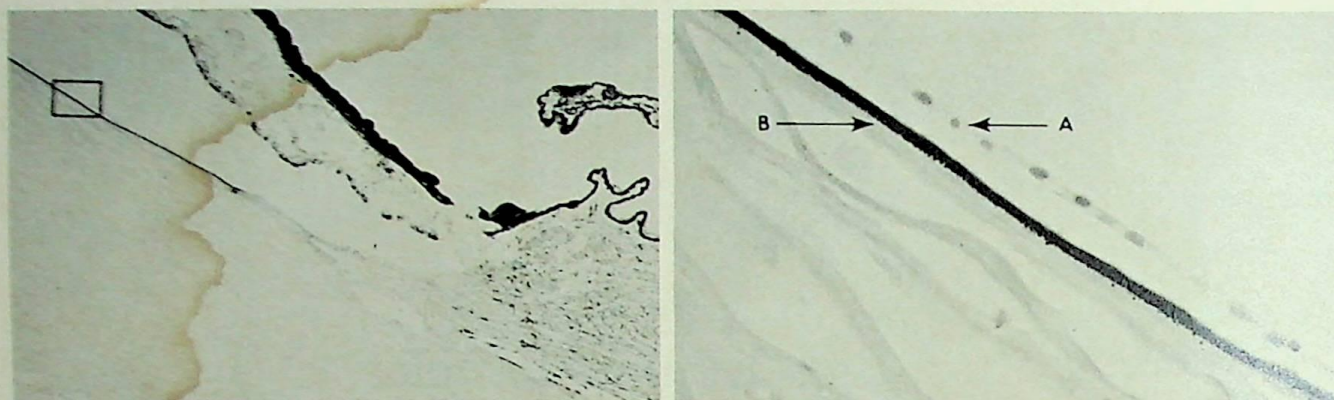


Fig. 1. *Left*, Corneal copper deposition at level of Descemet's membrane. (×64.) Inset is shown at higher magnification (*Right*). *Arrow* marked *A* points to corneal endothelium and *arrow* marked *B* indicates copper deposit in Descemet's membrane. (×640.)

(particularly in blue-eyed individuals), but slit-lamp biomicroscopy usually is required to establish its presence. Characteristically, the ring is most pronounced peripherally and tends to fade toward the center of the cornea—an attribute that has served to differentiate Kayser-Fleischer rings from corneal rings associated with other conditions, such as multiple myeloma in one case reported by Goodman and associates.[6] Electron microscopy and histochemical studies have shown that the rings consist of dense, nonuniform layers of unequal-sized copper granules separated by clear intervals of variable width in Descemet's membrane.[7] These collections of copper in Descemet's membrane constitute only a small percentage of the total corneal copper, as was demonstrated in one histochemically studied case in which corneal copper was 100 times the normal level.[8] The bulk of the total corneal copper is present in the stromal layer. However, no color change is produced by deposits in any layers of the cornea other than those in Descemet's membrane. This color change is presumably due to scattering and reflection of incident light and to photo-interference effects on the optical system created by the layers of copper granules. Specific variables including particle size, particle shape and regularity, particle zone size and density, number of zones, and distance between zones may account for differences in Kayser-Fleischer rings.[7]

Abnormally high concentrations of other metals, including zinc, iron, silver, and aluminum, have also been reported within the corneas of patients who have Wilson's disease, as studied histochemically at autopsy by means of spectrographic analysis.[9]

Pigmented corneal rings have been reported in patients with primary biliary cirrhosis,[10,11] chronic aggressive hepatitis with cirrhosis,[11] carotenemia with previously existing arcus senilis,[12] infestation with *Schistosoma japonicum* (presumably with a concomitant hereditary metabolic defect of hepatolenticular degeneration),[13] multiple myeloma with extremely high serum γ-globulin and copper concentrations,[6] African trypanosomiasis,[14] and during prolonged topical use of copper in trachoma and other eye conditions.[15,16] The pigmented ring seen in the cornea in primary biliary cirrhosis differs from the Kayser-Fleischer ring of Wilson's disease in that it is less dense and more tan than brown with a faint greenish tinge; it is not seen except by slit-lamp biomicroscopy. It is also of interest to note that with intraocular foreign bodies containing copper alloys (containing less than 85% copper) the copper will slowly diffuse into all parts of the eye, especially the cornea and lens. The original foreign body often disappears, and the classic picture includes the presence of a greenish-blue ring in the peripheral cornea, located mainly in Descemet's membrane. Foreign bodies containing more than 85% copper usually result in a severe suppurative inflammatory reaction with catastrophic consequences.

Relatively little has been published concerning the precise behavior of the Kayser-Fleischer rings with therapy of Wilson's disease. Some reports have documented a general decrease in or the disappearance of the rings under treatment with penicillamine, but many believe that little or no correlation exists between the clinical improvement of these patients and the changes in the Kayser-Fleischer rings.[17]

Another, lesser known, ophthalmologic manifestation of Wilson's disease is the sunflower cataract first described as "cataract like rays of the sun" or "Schein-katarakt" by Siemerling and Oloff in 1922.[18] The cataract does not impair vision and is not visible with the ophthalmoscope; slit-lamp biomicroscopy reveals a powdery deposit of brilliantly colored, variegated

material in browns, reds, blues, greens, and yellows immediately beneath the anterior and posterior lenticular capsules. Characteristically, the disk-shaped opacity, axially situated, with spokelike deposits radiating peripherally, resembles the petals of a sunflower. A second, more peripheral ring, concentric with the central deposit, has occasionally been reported. Cataracts situated solely posteriorly have not been reported in Wilson's disease but may occur in association with typical anterior subcapsular sunflower cataracts due to injuries involving the deposition of copper in the eye.[19]

Other ophthalmologic findings in Wilson's disease have been reported with notable infrequency. They include exotropic strabismus,[20] night blindness,[21] infrequent blinking,[22] suggestive pallor of the optic disks,[20,23] paralysis of upward gaze,[24] staircase pursuit movements on electro-oculogram studies,[20] and xerophthalmia.[25]

METHODS

Fifty-three patients with Wilson's disease were evaluated at the Mayo Clinic from 1952 through early 1977. Each patient underwent comprehensive neurologic and ophthalmologic examinations with serial follow-up evaluations in most cases, as noted in Table 1. Through detailed objective laboratory studies including determinations of serum copper, serum ceruloplasmin, and urinary copper excretion, and in some cases hepatic copper and radiocopper kinetic studies, all patients were considered to have unequivocal evidence of Wilson's disease. All ophthalmologic evaluations included slit-lamp examination and were conducted by one of the consultants in the Department of Ophthalmology at the initial visit and at all subsequent visits.

The patients are separated into three groups. Group 1 includes 35 patients who were symptomatic and were seen at the Mayo Clinic at or near the time of discovery of their disease and who therefore received their initial therapy at the Mayo Clinic; group 2 consists of 13 symptomatic patients whose condition was originally diagnosed at other institutions and who were started on appropriate therapy before examination at the Mayo Clinic. Group 3 is composed of five patients, all of whom were siblings of previously known patients with Wilson's disease and who were asymptomatic at the time of laboratory diagnosis.

Patients seen before 1958 were treated with British antilewisite (BAL or dimercaprol) administered intramuscularly. Penicillamine in the form of DL-penicillamine became available in 1958 and was used until the advent of D-penicillamine in 1962. These substances are water soluble and can be taken orally. In addition, all of the patients were given low-copper diets, vitamin supplements, and, in selected cases of severe hepatic impairment, oral vitamin K preparations and special hepatic diets.

RESULTS

Of the 53 patients studied, 35 (group 1) were symptomatic and were initially seen and treated at the Mayo Clinic. The mean age of these patients at the time of diagnosis was 24.3 years (range, 8 to 57 years) with a mean follow-up at the Mayo Clinic of 71.0 months (Table 1). Of these 35 patients, 34 (97%) had Kayser-Fleischer rings, all easily identifiable with slit-lamp examination. Typical Kayser-Fleischer rings appearing as full corneal circles were seen in 30 of 35 patients in group 1 (86%), and rings appearing as deposits in the superior and inferior corneal poles only were noted in 4 of the 35 patients (11%).

As a result of treatment, improvement occurred in the size and density of the Kayser-Fleischer rings among 18 of the 30 patients who had full rings at the time of diagnosis. Among the remaining 12, 3 patients were treated with intramuscular injections of BAL only, 3 were followed for less than a year, and 4 were lost to follow-up. Thus, 18 of 20 patients (90%) treated with penicillamine and followed for a year or more had improvement in the Kayser-Fleischer rings. Furthermore, 16 of these 18 patients (89%) had rings that improved from full corneal circles to only residual deposits in the superior and inferior corneal poles in a mean time of 37.3 months (range, 10 to 135 months) from the beginning of therapy with penicillamine. In addition, 12 of these 18 patients (67%) improved to having only superior corneal deposits in a mean time of 84.2 months (range, 8 to 197 months) from the start of penicillamine therapy. Total clearing of the Kayser-Fleischer rings was seen in 8 of the 18 patients (44%) in a mean time of 83.6 months (range, 12 to 163 months).

Of the four patients in group 1 with superior and inferior corneal deposits at the time of diagnosis, one patient showed improvement to only superior deposits in 29 months. The three other patients were followed for 0, 11, and 24 months without any notable change in the Kayser-Fleischer rings.

The one patient in group 1 (no. 26) who did not have Kayser-Fleischer rings at the time of diagnosis was only mildly symptomatic; his mother observed some lessening in coordination. Numerous examinations elsewhere in the 6 months before a definite diagnosis was made at the Mayo Clinic and resulted in the diagnosis of a "hyperkinetic and neurotic young man." The neurologic findings at the time of diagnosis

Table 1.—**Effect of Treatment on Kayser-Fleischer (KF) Rings and Sunflower Cataracts (SFC)**

Patient	Age at diagnosis (yr); sex	KF stage when first seen at Mayo Clinic	Regression of KF rings: To stage 2*	To stage 1*	To stage 0*	SFC†	Duration of follow-up, mo	Previous penicillamine treatment, mo
Group 1, symptomatic patients originally diagnosed and treated at Mayo Clinic								
1	28F	3	Yes (12)	. . .	. . .	No	13	
2	40M	3	Yes (23)	. . .	Yes (38)	Yes (23)	151	
3	29½M	3	. . .	. . .	. . .	No	14	
4	27M	3	. . .	. . .	. . .	No	23	
5	20F	3	. . .	. . .	. . .	Yes (no change)	28	
6	39M	3	Yes (50)	. . .	. . .	No	216	
7	49M	3	. . .	. . .	. . .	No	0	
8	21F	3	Yes (31)	Yes (63)	Yes (163)	No	156	
9	23F	3	. . .	. . .	. . .	No	0	
10	27½M	3	Yes (44)	Yes (145)	Yes (104)	No	153	
11	24½F	3	Yes (14)	Yes (18)	. . .	No	105	
12	12½M	3	Yes (25)	. . .	Yes (88)	No	137	
13	20M	3	Yes (10)	. . .	. . .	No	117	
14	32½M	3	Yes (63)	Yes (136)	. . .	No	192	
15	16½M	3	Yes (15)	Yes (54)	Yes (81)	No	104	
16	24M	3	. . .	. . .	. . .	No	9	
17	32½F	3	Yes (135)	Yes (146)	. . .	Yes (17)	146	
18	34½F	3	. . .	. . .	. . .	No	94	
19	19F	3	Yes (18)	Yes (52)	Yes (80)	Yes (33)	84	
20	10½M	3	Yes (15)	Yes (77)	. . .	No	77	
21	18½M	3	. . .	. . .	. . .	No	55	
22	8M	2	‡	. . .	. . .	No	11	
23	35F	3	. . .	Yes (8)	. . .	No	8	
24	17½M	3	Yes (33)	. . .	. . .	No	86	
25	13½M	2	‡	Yes (29)	. . .	Yes (14)	56	
26	11M	0	. . .	. . .	. . .	No	4	
27	57M	2	‡	. . .	. . .	Yes (no follow-up)	0	
28	24½F	3	. . .	. . .	. . .	No	14	
29	23½F	3	. . .	. . .	. . .	No	0	
30	14½M	2	‡	. . .	. . .	No	24	
31	23F	3	. . .	Yes (34)	Yes (12)	No	25	
32	19M	3	. . .	. . .	. . .	No	0	
33	21F	3	. . .	. . .	. . .	No	5	
34	17M	3	Yes (69)	Yes (197)	. . .	No	168	
35	17F	3	Yes (40)	Yes (80)	Yes (103)	No	209	
Subtotal		. . .	16	13	8	6	. . .	
Group 2, symptomatic patients (13) originally diagnosed and started on therapy elsewhere								
36	28M	3	. . .	. . .	. . .	No	0	48
37	45M	3	. . .	. . .	. . .	No	4	6§
38	27M	2	‡	. . .	. . .	No	0	27
39	23M	3	. . .	. . .	. . .	No	0	3
40	16½F	0	. . .	. . .	‡	No	0	77
41	11F	2	‡	. . .	. . .	No	0	19
42	26M	3	. . .	. . .	. . .	No	13	36
43	18F	3	. . .	. . .	. . .	No	0	9
44	15½M	3	Yes (34)	. . .	. . .	No	28	6
45	27M	0	. . .	. . .	‡	No	0	30
46	26M	1	. . .	‡	. . .	No	0	60
47	13½M	3	. . .	Yes (32)	Yes (56)	No	93	10
48	16F	1	. . .	‡	. . .	Yes (no follow-up)	0	10
Subtotal		. . .	1	1	1	1	. . .	

Table 1.—*Continued*

Patient	Age at diagnosis (yr); sex	KF stage when first seen at Mayo Clinic	Regression of KF rings: To stage 2*	To stage 1*	To stage 0*	SFC†	Duration of follow-up, mo	Previous penicillamine treatment, mo
			Group 3, asymptomatic patients (5)					
49	6F	0	. . .	. . .	. . .	No	134	
50	33½M	0	Appeared 20 mo after patient first seen		Yes (8)	No	119	
51	5F	0	. . .	. . .	. . .	No	35	
52	5M	0	. . .	. . .	. . .	No	75	
53	23F	0	. . .	. . .	. . .	No	11	
Subtotal		. . .	0	0	1	0	. . .	

*Numbers in parentheses indicate time from onset of treatment, mo.
†Numbers in parentheses indicate time from onset of treatment to resolution, mo.
‡Kayser-Fleischer ring was already present at this stage when patient was first seen.
§Patient was treated with BAL for 48 mo before penicillamine therapy.

were minimal bilateral dystonia, more pronounced in the upper extremities, and minimal incoordination and decrease of the alternate motion rate of the extremities. No tremor was present. He had a markedly enlarged liver along with laboratory evidence of hepatic dysfunction. Decreased serum ceruloplasmin concentration and increased urinary excretion of copper, along with radiocopper kinetic studies, confirmed the diagnosis.

All of the 13 patients in group 2 had been treated initially elsewhere as recorded in Table 1. In this group, 11 of the 13 patients had Kayser-Fleischer rings at the time of our examination. The two patients without rings (no. 40 and 45) had previously been treated with penicillamine for 77 and 30 months, respectively, and had a history of typical full-circle Kayser-Fleischer rings before the start of therapy. Only 3 of the 13 patients in this group were followed for a year or more, and 2 of the 3 had improvement in their rings. The remaining patient (no. 42) showed no change in the rings in 13 months.

None of the five asymptomatic patients in group 3 had Kayser-Fleischer rings at the time they were first seen (Table 1). One of the five (no. 50) had Kayser-Fleischer rings in the superior and inferior poles 20 months after the initial normal slit-lamp examination. Penicillamine therapy had been withheld because of borderline laboratory evidence of Wilson's disease at his initial evaluation.

Sunflower cataracts were observed in 7 of the total 53 patients, including 6 of 35 patients in group 1 and 1 patient from group 2. The mean age of these patients at the time of diagnosis of the cataracts was 28.4 years (range, 13½ to 57 years), and all of them had associated Kayser-Fleischer rings throughout the time the cataracts were present. Bilaterally symmetric involvement was noted in five of the seven patients, one of whom had deposits in both the anterior and the posterior subcapsular layers. One patient had bilateral anterior subcapsular deposits, more pronounced in the right eye, and another had involvement of the anterior lenticular epithelium in the left eye only. Total resolution of the sunflower cataracts was noted in four of the seven patients in a mean time of 22.0 months (range, 14 to 33 months). Two of the remaining patients had no follow-up at the Mayo Clinic, and the other showed no change in lenticular deposits over 28 months and died at 34 months in hepatic failure.

Other ophthalmologic abnormalities were notably infrequent: they occurred in only 3 of 53 patients.

One patient (no. 2), reported previously,[26] was found on initial examination to have bilateral mild exophoria and poor convergence, which persisted throughout his follow-up. One year later, Kayser-Fleischer rings developed and he was given DL-penicillamine. After 21 months of therapy, he experienced bilateral optic neuritis with congestion of the optic disks, loss of central vision to 20/200 in each eye due to central scotomas, sheathing of several arterioles near both optic disks, and a splinter hemorrhage temporal and inferior to the left optic disk. Penicillamine therapy was continued at half the original dose and no steroids were administered. Over the next 6 months the optic neuritis gradually resolved, the visual acuity returned to normal, and there were residual findings only in the form of persistent sheathing of each inferior macular arteriole.

One patient (no. 9) complained of decreased ability to read and occasional diplopia. She had paralysis of accommodation and ataxic movements of the eyes.

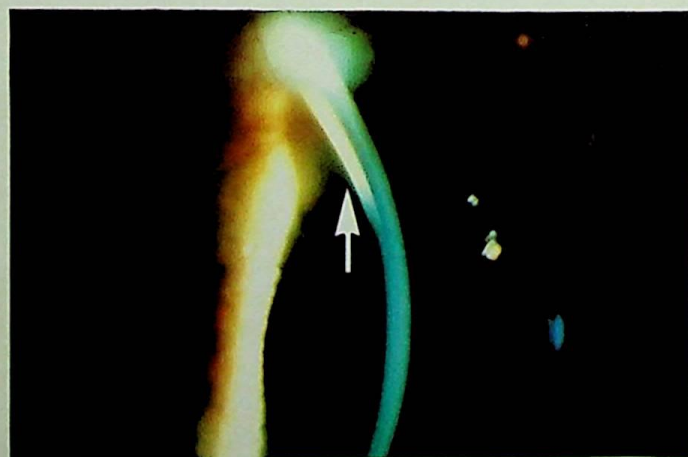
No palsies of the extraocular muscles could be demonstrated. She died a few months later.

Patient no. 28 was exophoric at the initial examination and had bilateral mild blepharoptosis and minimal bilateral paresis of the orbicularis oculi muscles. On follow-up examination 14 months after the start of penicillamine therapy, all of these deficits had reverted to normal.

DISCUSSION

Wilson's disease is one of the few inborn errors of metabolism in which specific medical therapy can so dramatically reverse a progressively deteriorating course. Untreated, the disease is universally fatal. It is thus of utmost importance to make the correct diagnosis as early as possible. Toward this end, the presence and absence of certain ophthalmologic findings can be of great assistance.

As shown above, of the symptomatic patients at the time of diagnosis, 97% had Kayser-Fleischer rings easily seen on slit-lamp biomicroscopy. This finding emphasizes the importance of routinely examining by slit-lamp biomicroscopy those patients who have evidence of tremor, dystonia, rigidity, dysarthria, or hepatic decompensation of uncertain origin, particularly patients with brown irides, in whom the corneal rings may be extremely difficult to appreciate with the naked eye. Furthermore, the absence of Kayser-Fleischer rings on slit-lamp biomicroscopy of a symptomatic patient should lead the clinician to question seriously the diagnosis of Wilson's disease.

At the same time, it must be emphasized that, of the five asymptomatic siblings of patients with previously known Wilson's disease, none had Kayser-Fleischer rings at the time of diagnosis. This substantiates the importance of screening asymptomatic siblings with serum copper, serum ceruloplasmin, and urinary copper excretion studies even when Kayser-Fleischer rings are absent, as suggested by Sternlieb and Scheinberg.[27] At times it is necessary to perform a liver

Color Plate. *Upper Left* and *Right*, Kayser-Fleischer stage 3 corneal ring shows full-circle corneal involvement as classically described. This also demonstrates variation in appearance of full Kayser-Fleischer ring in two patients. *Lower Left*, Kayser-Fleischer stage 1 corneal ring shows involvement at superior corneal pole only. *Lower Right*, Slit-lamp photograph of Kayser-Fleischer stage 1 corneal ring shown in *Lower Left*. *Arrow* indicates Kayser-Fleischer ring as visualized with slit-lamp biomicroscopy.

biopsy for copper analysis or a radiocopper kinetic study.

Improvement in the Kayser-Fleischer rings was seen in a high percentage (87%) of patients treated with penicillamine and followed for a year or more after the onset of therapy. Moreover, the improvement follows a specific pattern along a continuum with four easily recognizable and reproducible Kayser-Fleischer stages as follows: stage 0—no identifiable corneal rings; stage 1—corneal rings at the superior poles only; stage 2—corneal rings at the superior and inferior poles; and stage 3—full-circle corneal rings encompassing the entire periphery of each cornea as classically described (Color Plate, upper). The vast majority of patients with Wilson's disease are in stage 3 at the time of diagnosis. Treatment with penicillamine results in gradual resolution of the rings through stages 2, 1, and 0. Of the 40 patients in groups 1 and 3 who were seen before the initiation of penicillamine therapy, 5 presented with stage 2 rings. Included within this group was one of the asymptomatic patients who had had a negative slit-lamp examination 20 months previously. All of these five patients had initial hepatic symptoms; and at the time of recognition of the Kayser-Fleischer rings their clinical picture was predominantly one of hepatic disease with minimal or no neurologic abnormalities. These data suggest that corneal and intracerebral copper deposition occurs with some degree of synchrony, after the binding sites for copper in the liver have been saturated. The data also suggest that the deposition of copper within Descemet's membrane proceeds from Kayser-Fleischer stage 0 through stages 1 and 2 before reaching stage 3, at which time the diagnosis of Wilson's disease is usually made. We suspect that earlier diagnosis of Wilson's disease may be possible in some cases if stage 1 and 2 rings are recognized initially, particularly in patients with predominantly hepatic findings. The region of the superior corneal pole is the most sensitive area for the early detection of Kayser-Fleischer rings and should be examined carefully in screening all patients for Wilson's disease, even when the rest of the slit-lamp examination is apparently normal (Color Plate, lower).

The mechanism for the pattern of deposition of Kayser-Fleischer rings and the improvement with therapy is not known. An attractive hypothesis is as follows. The systematic layering of copper granules observed within Descemet's membrane in previous electron microscopy studies,[7] the clinical picture resulting from the diffusion of copper foreign bodies in the eye as discussed above, and the solubility characteristics of ionic copper loosely bound to albumin make it very likely that copper is initially taken up in the aqueous humor and enters the cornea by diffusion through its endothelial layer. Within the cornea, the movement of water-soluble substances proceeds from posterior to anterior, largely as a result of the osmotic gradient, which is a function of the evaporation of tears from the surface of the cornea. It is evident that such evaporation of tears is much less pronounced at the superior and inferior corneal poles and least at the superior pole because the eyelids partially cover these areas.

One can postulate that a relative stagnation of solvent flow in the superior poles allows the original precipitation of copper in the superior and inferior regions of Descemet's membrane and that flow is too rapid in the other corneal areas to allow as much copper deposition initially. Under treatment with penicillamine, the process of "decoppering" the cornea presumably also proceeds as a function of corneal solvent flow patterns. As more penicillamine is available for chelation of copper, a greater transport of chelated copper may occur in the areas of greater flow, and this may explain the highly consistent regression pattern of the Kayser-Fleischer rings described above. Other, less likely, contributing factors, which may vary with the amount of relative corneal exposure, are temperature, light, and concentration of oxygen. It is possible that these factors in some way affect the solubility properties of copper within Descemet's membrane or, even less likely, that Descemet's membrane differs in some subtle histochemical parameters at the poles and that this accounts for differences in the precipitation of copper.

The incidence of sunflower cataracts in this study (17% of symptomatic patients seen before therapy) is almost double the incidence suggested by collective data from smaller series reported in the literature. None of the cataracts was visible without the aid of the slit lamp and none inpeded vision, findings that confirm two previously reported observations.[28] Interestingly, two patients had markedly asymmetric sunflower cataracts, including one unilateral case, only rarely reported in the past. Another patient, who had bilateral posterior (in addition to anterior) lenticular deposits, constitutes the only reported case of posterior lens deposition in a patient with Wilson's disease. In general, the sunflower cataracts tended to clear much more rapidly than did the Kayser-Fleischer rings under treatment with penicillamine and were noted only in association with Kayser-Fleischer stages 2 and 3 rings.

Also helpful in the diagnosis of Wilson's disease is the remarkable absence of certain other ophthalmologic findings such as nystagmus, cranial nerve palsies, and other extraocular movement disorders that might be expected in a disease capable of producing such profound general neurologic abnormalities. In particular, the absence of nystagmus may be helpful in differentiating this disease from multiple sclerosis (a disease for which Wilson's disease is sometimes mistaken, as evidenced by the historic synonym "pseudosclerosis of Westphal and Strümpell").[18]

Finally, the possibility that optic neuritis is a common side effect of penicillamine therapy was not substantiated in this study. Despite extensive use of this medication in all patients treated since 1958, optic neuritis developed in only one patient and it cleared despite continuation of therapy with DL-penicillamine.[26]

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Second Pan American Symposium on Hypertension—Part III

Pathogenic Factors Involved in Renovascular Hypertension

STATE OF THE ART

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The complex hormonal action of angiotensin II in the long-term control of blood pressure or sodium metabolism, or in renal hypertension, is not completely understood. Structure-activity relations with analogues of angiotensin II gave information about the functions responsible for pressor and myotropic response in the molecule that led to the synthesis of competitive antagonists of this hormone. These antagonists, however, show variable agonist/antagonist ratios in different species or different tissues of the same species. This fact necessitates further work to induce tissue specificity. Although des-Asp^{1}-angiotensin II ("angiotensin III") has been recognized as a hormone, its exact role in the biosynthesis of aldosterone is yet to be discovered. The antagonists such as des-Asp^{1}-[Ile^{8}]-angiotensin II or des-Asp^{1}-[Thr^{8}]-angiotensin II have provided important leads in this direction. Many of the biologic effects of angiotensin I have been attributed to its conversion to angiotensin II by the converting enzyme. Recent investigations indicate that angiotensin I itself may play a direct role; however, most of these studies were carried out by inhibiting the converting enzyme activity with peptides obtained from the venom of *Bothrops jararaca*. Since these peptides also potentiate bradykinin action, the observed biologic activities could be caused by either angiotensin I or bradykinin. Besides, converting enzyme is no longer thought to be a single enzyme and its nature varies from species to species and from tissue to tissue in the same species. Renin inhibitors related to renin substrate or pepstatin are not freely soluble in plasma and are not effective under physiologic conditions. This points to the importance of renin inhibitors isolated from kidney or other natural sources. Thus, although the renin-angiotensin system appears to be an integral part of the problem of hypertension, characterization of various converting enzymes, roles of extrarenal renin, isorenin, tonin, and brain-renin, and the involvement of other humoral, neurogenic, and immunogenic factors should be pieced together to get a clear picture of the hypertension problem.

There are many conceptual problems relating to the dynamic state of renal hypertension. The idea that the renin-angiotensin system is a sole requisite for the hypertensive state has waxed and waned for many years. It has long been accepted, however, that renin is not a necessary etiologic factor for the development of necrotizing arteriolar lesions. In 1973, Giese[1] reviewed this aspect in detail and concluded that activation of the renin-angiotensin system is not a necessary condition for the emergence of necrotizing arteriolar lesions in hypertensive disease, but that it could be a contributing factor. However, most of these conclusions are based on experiments using impure kidney extracts, and it is therefore difficult to determine the exact role of renin.

In 1949, Page[2] proposed the mosaic theory of blood pressure control involving several humoral factors, volume reactivity, cardiac output, and neural components; however, complete quantitative data are not available concerning the interrelationship of these systems. Guyton and associates[3] have attempted quantitation between volume and angiotensin but have placed little emphasis on all these other systems in their computer model.

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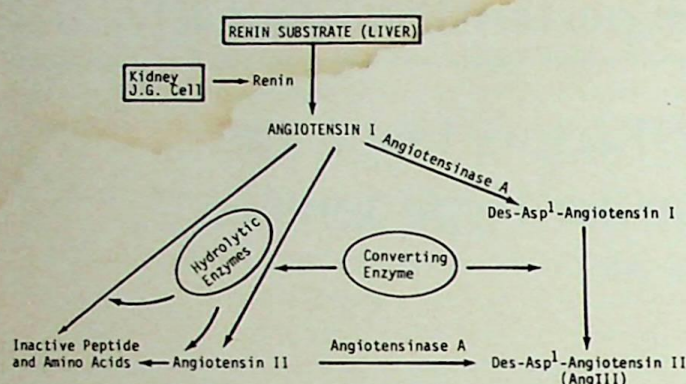
Fig. 1. Renin-angiotensin system.

Much research has been directed toward the renin-angiotensin system, often without taking into account other possible contributing factors. The present complexity of the system is shown in Figure 1.

For the past 30 years, scientists have attempted to find ways to block the renin system. As more was learned about this system in the 1950's, it became obvious that one could identify ways to block the system by finding renin inhibitors, converting-enzyme inhibitors, or competitive antagonists to angiotensin I or II. Since 1969,[4] when it was shown that a metabolite of angiotensin II, des-Asp[1]-angiotensin II ("angiotensin III"), has an activity of its own, it has also become important to find specific inhibitors for this heptapeptide.

ANTIHYPERTENSIVE EFFECT OF A PHOSPHOLIPID RENIN INHIBITOR FROM KIDNEY

The first renin inhibitor of significance was reported by Sen and associates[5] and was used in hypertensive rats. It is unfortunate that this substance was not useful in other animals and, consequently, the early work was not reproduced by other investigators. However, in recent years this substance has been prepared synthetically in several other laboratories and it has been shown that it not only inhibits renin but is also useful for affinity chromatography of renin.[6] It is also extremely interesting that the results first reported in our laboratory about the effects of this substance in hypertensive rats[7,8] are very similar to those now being reported on the use of converting enzyme inhibitors or angiotensin antagonists. Reviewing the results from this work, we can see from Figure 2 the effects of this renin preinhibitor on acutely hypertensive rats.[7,8] It is significant here that, in animals that had pressures of 200 mm Hg with elevated renin levels, the blood pressure was reduced but not to normotensive levels. After cessation of injection of this material, the pressure again rose to the preinjection hypertensive levels. It is also interesting to note that renin levels likewise increased after the cessation of injection to levels even higher that those before the preinhibitor was injected.

Fig. 2. Effect of phospholipid renin-preinhibitor on plasma renin activity in acute hypertensive rats.[7,8]
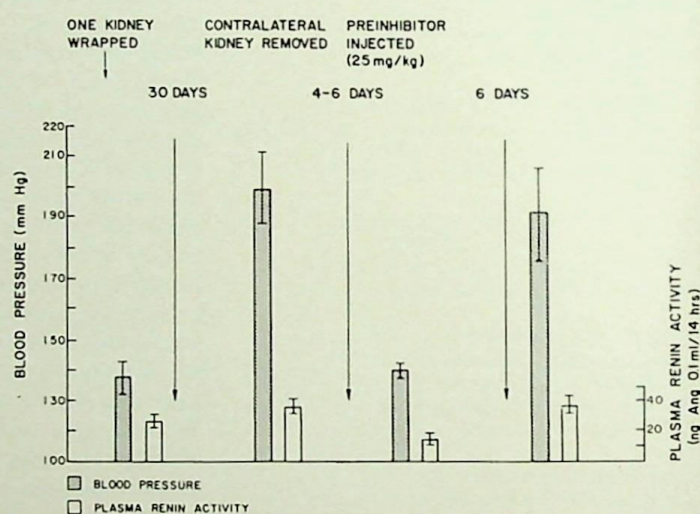
Fig. 3. Effect of phospholipid renin-preinhibitor on plasma renin activity in perinephritic rats.[7,8]

Similar results were also obtained when Sen and associates[7,8] injected the preinhibitor into animals made hypertensive by a perinephritic wrap on the kidneys (Fig. 3). The renin levels in these animals were slightly lower than those of animals treated with the renal artery clip. However, the blood pressure response to renin blockade seemed to be just as significant as that of the clipped animals. Animals with hypertension of prolonged duration likewise responded to this substance with a reduction in blood pressure. It should be noted that the renin levels in these animals were not quite as high as in those with hypertension of shorter duration. It did decrease after the injection of the inhibitory material and again increased after the cessation of the injection; however, renin activity in these animals was as high as had been

obtained in animals that had more acute hypertension. These results were not well accepted at the time of publication partly because others had difficulty in preparing the phospholipid and also because the substance appeared to be active in rats but had little activity in dogs. The reason for its high activity in rats is perhaps related to the presence of very high levels of phospholipase A, which is necessary to convert the phospholipid preinhibitor into an active form.

ANTAGONISTS OF THE PRESSOR AND ALDOSTERONE-RELEASING EFFECTS OF ANGIOTENSIN II

Because of the possibility that the phospholipid may have other unknown activities which may be responsible for the observed reduction in blood pressure, it was necessary to continue to search for other renin inhibitors or angiotensin antagonists. To develop angiotensin inhibitors, the first approach was a thorough study of structure-activity relationships of angiotensins. This aspect has been recently reviewed.[9,10] As a result of these studies, we were able to show that the side group in position 8 on angiotensin must be responsible for the transmission of the information which caused smooth muscle contraction. This information led to the development of the 8-substituted analogues that are competitive inhibitors of angiotensin. None of the other substitutions in the angiotensin molecule produced competitive antagonists. Much speculation has been made in recent years about the mode of binding of angiotensin as well as its mode of transmission of the response.

Properties of the analogues that seem to be most useful will be discussed here as well as the effect of sarcosine in position 1, which potentiates the activity of both angiotensin inhibitors as well as of the agonist itself. Indeed, the introduction of sarcosine does not produce an inhibitory molecule; it potentiates the biologic activities already existing in the molecule. Tables 1 and 2 compare the biologic properties of 8-alanine, 8-isoleucine, 8-threonine, and 8-O-methylthreonine derivatives of angiotensin II. It is most unfortunate that [1-sarcosine, 8-alanine]-angiotensin II was made available to so many people so rapidly without first analyzing its merits as an antagonist. It is now known that this analogue has high agonist properties but is manyfold less potent as an antagonist. It appears that some of the recently synthesized analogues are far superior (Tables 1 and 2), and that the large amount of research that has been carried out with [1-sarcosine, 8-alanine]-angiotensin II may have to be repeated on some of these recent analogues.

Our aim has been to produce analogues with fewer side effects but with increased potencies and binding affinity to the receptor. For this reason, we synthesized [1-sarcosine, 8-isoleucine]-angiotensin II[11] and [1-sarcosine, 8-threonine]-angiotensin II.[12] These analogues were found to have very high dose-ratio and binding affinity.[11-13,17-19] As compared to these analogues, [1-sarcosine, 8-alanine]-angiotensin II is a very weak antagonist.[17,18] [1-Sarcosine, 8-O-methylthreonine]-angiotensin II has an extremely high dose-ratio and is a strongly competitive inhibitor of angiotensin II.[13] However, it has the same undesirable high agonist properties as do the 8-isoleucine or 8-alanine derivatives. On the other hand, the 8-threonine analogue has very low agonist properties, for both direct myotropic activity and for catecholamine-releasing effect[13,14,17,19] (Table 1). We have synthesized a large number of other analogues, some of which are more related structurally to phenylalanine in position 8. An example of the latter is [8-cyclohexylalanine]-angiotensin II.[11] It is a good antagonist; however, the dose-response curves suggest that, at least at higher dose levels, this substance is a noncompetitive antagonist. It, likewise, as do several of the other compounds, has a high agonist component that makes it useless for physiologic experiments.

Table 1.—**Intrinsic Activities of Angiotensin II Analogues Relative to Angiotensin II***

Analogue	Pressor activity in ganglion-blocked vagotomized rats	Myotropic activity in rabbit aortic strips	Secretory activity in isolated cat adrenal medulla	Secretory activity in isolated cat adrenal cortex
Angiotensin II	100.0	100.0	100.0	100.0
[Ala⁸]	0.1	0.1	25.0	2.0
[Ile⁸]	0.63	<5.0	25.0	2.5
des-Asp¹-[Ile⁸]	0.1	0.1	0.0	10.0
[Sar¹, Ala⁸]		0.5	3.0	0.5
[Sar¹, Ile⁸]	1.0	1.0	3.0	1.0
[Sar¹, Thr⁸]	0.6	0.5	0.1	1.0
[Sar¹, Thr(Me)⁸]	0.48	0.5	0.1	0.5

*For details of the data in this Table, see references 10-16.

Table 2.—**Comparative Agonist and Antagonist Effects of Angiotensin II Antagonists Infused Into Ganglion-Blocked Vagotomized Rats at a Dose Level of 250 ng/min per kg**

Angiotensin II analogue	Increase in blood pressure during analogue infusion, mm Hg ± SEM			Angiotensin II $ED_{20} \times 10^{-9}$ ± SEM		
	3 minutes	10 minutes	30 minutes	Before infusion of analogue	During infusion of analogue	Dose-ratio*
[Sar^1, Ala^8][17,18] (P-113)	15.11 ± 1.48	16.88 ± 1.87	17.44 ± 1.66	1.89 ± 0.19	14.16 ± 1.88	7.92 ± 1.21
[Sar^1, Ile^8][11,17,18]	17.81 ± 0.99	18.27 ± 1.72	14.81 ± 2.16	2.19 ± 0.15	59.18 ± 15.03	27.79 ± 6.25
[Sar^1, Thr^8][12,13,17-19]	9.46 ± 0.79	9.66 ± 2.00	9.20 ± 4.26	1.71 ± 0.26	44.55 ± 8.20	26.91 ± 3.30
[Sar^1, Thr(Me)^8][13]	13.82 ± 0.98	15.88 ± 0.85	15.06 ± 1.63	1.55 ± 0.10	95.26 ± 23.83	62.52 ± 14.93
des-Asp^1-[Ile^8][17,18]	4.66 ± 1.33	9.66 ± 2.00	12.66 ± 2.77	1.65 ± 0.35	2.80 ± 0.92	1.69 ± 0.44

*ED_{20} of angiotensin II was determined before infusion of the analogue and during infusion of the analogue, and the dose-ratio was calculated as ED_{20} of angiotensin II during infusion of the analogue divided by ED_{20} of angiotensin II determined before infusion of the analogue.

Sarcosine introduced into the 1 position increases the potency of both the angiotensin agonist[20] and the angiotensin antagonist molecules. Introduction of sarcosine into position 1 of angiotensin II increases the pressor activity as well as the myotropic activity.[20] Various experiments have demonstrated that it does, indeed, bind to the same receptor as angiotensin II and exhibits a similar response in all systems thus far tested. It has been reported by Fredlund and co-workers[21] that [1-sarcosine]-angiotensin II is a more potent agonist for the release of aldosterone.

Complete removal of aspartic acid, as first shown by Blair-West and collaborators,[4] does not reduce the aldosterone-stimulating activity of angiotensin. However, this change considerably reduces the myotropic and vasopressor activities. In order to study the effect of chain-length on the specificity of inhibition of angiotensin II activities, we synthesized des-Asp^1-[Ile^8]-angiotensin II,[15,22] des-Asp^1-[Thr^8]-angiotensin II,[23,24] and des-Asp^1-[Ala^8]-angiotensin II.[25] Although these analogues do not inhibit the myotropic or vasopressor activities of angiotensin II to any significant degree, they are rather specific for inhibiting the aldosterone-releasing activities.[15,22-29] However, des-Asp^1-[Ala^8]-angiotensin II and des-Asp^1-[Ile^8]-angiotensin II also have rather high agonist properties for the release of aldosterone, whereas the threonine-substituted compound has very low agonist property.

Results of the infusion studies in ganglion-blocked vagotomized rats are given in Table 2.[13,17-19] At 3 minutes, 10 minutes, and 30 minutes, [1-sarcosine, 8-threonine]-angiotensin II certainly has much less agonist activity than either [1-sarcosine, 8-alanine]-angiotensin II or [1-sarcosine, 8-isoleucine]-angiotensin II. A comparison of dose-ratios in rats shows that [1-sarcosine, 8-threonine]-angiotensin II has the highest dose-ratio of the three compounds and is almost four times as potent as [1-sarcosine, 8-alanine]-angiotensin II in this experiment. The O-methylthreonine derivative has a dose-ratio of approximately 60 but its agonist activity is comparable to that of [1-sarcosine, 8-isoleucine]-angiotensin II.[13] That [8-alanine]-angiotensin II is a good agonist for the release of catecholamines was first demonstrated on the isolated cat adrenal gland.[16] Later studies indicated that a part of the initial pressor activity of these antagonists can be blocked in vivo with alpha blockers.[13,17-19] A comparison of [1-sarcosine, 8-alanine]-angiotensin II and [1-sarcosine, 8-threonine]-angiotensin II in isolated cat adrenal medulla indicated that the secretory activity of [1-sarcosine, 8-threonine]-angiotensin II is 30 times less than that of the 8-alanine analogue,[13,14] and that the 8-threonine analogue acts as a potent competitive antagonist for catecholamine secretion.[14,16]

Recent studies by Bravo and associates[30] in sodium-depleted, trained, unanesthetized dogs indicated that, as compared with [1-sarcosine, 8-alanine]-angiotensin II and [1-sarcosine, 8-isoleucine]-angiotensin II, [1-sarcosine, 8-threonine]-angiotensin II was found to be the most potent antagonist in reducing arterial blood pressure. Further, [1-sarcosine, 8-threonine]-angiotensin II was found to have no agonist effect on vascular smooth muscle in doses with significant antagonistic activity, whereas both [1-sarcosine, 8-alanine]-angiotensin II and [1-sarcosine, 8-isoleucine]-angiotensin II initially provoked significant increases in arterial blood pressure before exerting their antipressor action. Also, in marked contrast to [1-sarcosine, 8-alanine]-angiotensin II and [1-sarcosine, 8-isoleucine]-angiotensin II, the threonine analogue had no significant agonist activity on the adrenal cortex even when given in very large doses (that is, 10 μg-kg per minute).

EFFECTS OF ANGIOTENSIN ANTAGONISTS IN VARIOUS FORMS OF EXPERIMENTAL HYPERTENSION

In 1971, Brunner and co-workers[31] and Pals and co-workers[32,33] determined the effects of the [Sar^1, Ala^8]-angiotensin II on blood pressure of rats that had been hypertensive for about 6 weeks, and Brunner and associates discussed the effects on rats that had renal hypertension caused by clamping one renal artery with the opposite kidney intact (two-kidney model) or removed (one-kidney model). They determined that the antagonist as well as angiotensin antiserum would reduce blood pressure in the two-kidney rats but not in one-kidney hypertensive animals. From this they concluded that the mechanism of hypertension was different in these animals. Our results, as well as those of Bing and Nielsen,[34] are somewhat at variance with this. When we used [1-sarcosine, 8-isoleucine]-angiotensin II, we were able to reduce blood pressure in the one-kidney animals with hypertension of 4- to 8-weeks' duration.[35] If the hypertension lasted for 30 weeks, we were able to reduce the blood pressure only to a moderate degree with [1-sarcosine, 8-isoleucine]-angiotensin II.

Sweet and co-workers[36] reported on the use of [1-sarcosine, 8-isoleucine]-angiotensin II in conscious animals and reported that in dogs with hypertension of short duration, the pressure dropped rather precipitously, whereas it was difficult to lower the blood pressure in animals that had had hypertension for more than 8 days.

In 1973, Pals and Masucci[37] reported that the amount of decrease in blood pressure obtained by the use of [1-sarcosine, 8-alanine]-angiotensin II in hypertensive animals was directly proportional to the renin level in the hypertensive animals. Johnson and co-workers,[38] using [1-sarcosine, 8-alanine]-angiotensin II as a competitive antagonist, also were unable to show a significant effect on the blood pressure in conscious dogs that had been hypertensive for 2 to 7 weeks. We,[35] likewise, reported in 1973 that conscious rats and dogs that had had hypertension from 10 to 15 days did not have a reduction in blood pressure when given the 8-isoleucine analogue.

Recently, Ferrario and associates[39] studied the effects of angiotensin antagonists in various forms of experimental arterial hypertension in conscious dogs. The results indicated that continuous infusion of these angiotensin blockers produced a partial lowering of blood pressure only during the acute phase of one-kidney and two-kidney renal hypertension. At this early stage of hypertension, part of the increase in arterial pressure may, therefore, be renin dependent. On the other hand, the response of the elevated blood pressure to additional infusions of the blockers became negligible as hypertension progressed to a more chronic phase, at a time when the concentration of renin in peripheral plasma was not above normal values. Likewise, these angiotensin antagonists had no effect on the increased blood pressure of dogs that had hypertension caused by perinephritis induced by cellophane wrapping, an established method leading to a more chronic and benign form of renal hypertension. Similarly Masaki and associates[40] studied the course of arterial pressure and the effect of [1-sarcosine, 8-threonine]-angiotensin II in conscious dogs. Two-kidney hypertension was produced by a two-step procedure involving complete occlusion of a renal artery 2 weeks after it was partially constricted. Intravenous infusion of [Sar^1, Thr^8]-angiotensin II caused arterial pressure to decrease during the acute but not the chronic phase of renal hypertension. In this latter phase, plasma renin activity had returned to control values.

In 1973, Gavras and collaborators[41] showed that [1-sarcosine, 8-alanine]-angiotensin II produces a marked decrease in blood pressure even if plasma renin is not at an increased level. They were the first to show that the blood pressure could be reduced to normal levels with these analogues only when the animals were depleted of sodium. They concluded at that time that the importance of angiotensin for maintaining arterial pressure is largely determined by its relation to the available plasma sodium or the extracellular fluid volume, or both. They have not, however, measured extracellular fluid volume in any of their animals or patients. Numerous investigators have continued using this derivative in humans with the hope of using it as a diagnostic tool. A recent report by Gavras and associates[42] has shown that they now recognize that [1-sarcosine, 8-alanine]-angiotensin II does, indeed, have agonist properties. They point out that they are able to decrease blood pressure in patients to a greater extent using the converting enzyme inhibitor than using [1-sarcosine, 8-alanine]-angiotensin II, and they speculate that the difference between these two blocking substances is that [1-sarcosine, 8-alanine]-angiotensin II has agonist properties.

EFFECT OF ANTIBODIES TO RENIN IN EXPERIMENTAL RENAL HYPERTENSION

The large number of experiments carried out using competitive antagonists of angiotensin, antagonists of converting enzyme, and, to a lesser extent, renin

antagonists, have not completely clarified the role of the renin-angiotensin system. Indeed, the results of these experiments suggest that renin does participate in the control of blood pressure, a finding that we had guessed all along; the fact that the response is greater in a sodium-depleted animal is not at all surprising. Indeed, if one completely depletes a normal animal of sodium, forcing it to become renin-dependent, the animal will also respond to the blockade of renin by reduction in blood pressure. Furthermore, none of the authors who have attempted to explain hypertension solely on the basis of volume and renin have made any attempt to explain why the blood pressure is volume-dependent if the renin system is blocked. If the blockade of the renin system is complete and there are no other contributing factors, then why does the blood pressure not return to normotensive levels? This anomaly was demonstrated a number of years ago by Wakerlin[43] and then by Deodhar and associates.[44]

After the injection of acetylated renin into a hypertensive dog that had been hypertensive for 6 years, the dog responded, as the antibody titer increased, by a reduction to a normotensive level of the blood pressure, and as the renin titer became reduced the blood pressure was again increased. This experiment was repeated in the same dog and the phenomenon was shown to be reproducible. This animal was not sodium-depleted, and to explain the results of angiotensin II antagonists and converting enzyme inhibitors we must consider that either there are other substances present in the kidney that have an effect on blood pressure leading to an effect on blood volume or that angiotensin blockade is not complete in any of the situations described.

ISOLATION OF NEW MACROMOLECULES FROM KIDNEY OR URINE

Skeggs and associates[45] have recently been able to reduce the blood pressure of rats by administering antibodies to a protein fraction of kidneys freed of renin by affinity chromatography. We have continued to look for additional substances that may cause hypertension and, accidentally, have discovered a substance in human urine[46,47] that will cause an increase in blood pressure when injected into rats. The pressure remains elevated as long as we continue to inject the material, and after withdrawal the pressure slowly reverts to the normotensive level. The origin of this material is unknown other than that we obtain it from urine. It is a high-molecular-weight protein of about 20,000 daltons. It has been purified by several forms of chromatography, which suggests that it does not contain any small molecular adsorbed materials and that its activity derives from the protein substance itself. The activity is destroyed by proteolytic enzymes. The substance causes an increase in plasma volume as well as a reduction in sodium excretion. The cause of the hypertension is still unknown but expanded volume undoubtedly plays a role.

CONCLUSIONS

We do not intend to imply that we believe that sodium does not play a role in renovascular hypertension. However, the following points must be kept in mind as we attempt to piece the hypertension mosaic together:

1. We must be acutely aware of the properties of blocking agents used. Angiotensin antagonists have many activities; one property of angiotensin may be reduced while another may be potentiated.

2. Converting enzyme inhibitors potentiate bradykinin. Because kininase II is identical with the angiotensin I converting enzyme, these properties cannot be separated.

3. Angiotensin I and des-Asp^1-angiotensin II ("angiotensin III") may have a role in increasing blood pressure.

4. The roles of extrarenal renin, isorenins, tonin, and brain renin have not been established.

5. We should not overlook the possibility that there may be additional unknown factors involved.

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Half-Life of Circulating Renin Under Different Experimental Conditions

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The half-life of circulating renin was studied in normal rats and in rats with a single kidney that was ischemic. The resulting disappearance curve represented the sum of two exponentials. The average half-life of the fast component was 11.5 minutes for normal rats, 11 minutes for rats with mild renal ischemia, and 8 minutes for rats with severe renal ischemia. The mean half-life of the slow component was 67 minutes in normality, 84 minutes in mild ischemia, and 121 minutes in severe ischemia. Also, the calculated proportion of the slower component was different for each group—60.3% in normality, 68.2% in mild ischemia, and 82.2% in severe ischemia. The results suggest that more than one kind of renin may be produced and released by the kidney, and also that renal ischemia may modify the normal metabolism of renin.

Since the initial experiments of Houssay and associates[1] in 1942, several reports[2-6] related to the rate of disappearance of endogenous or exogenous renin have been published. According to them, at least two renin components with different half-times of disappearance were found.[4-6] The authors suggested that a compartmental distribution could be the explanation of these findings.

We[7] previously reported that renin and a purified fraction of kidney extract called sustained pressor principle have a different half-life in blood. In the present study, the disappearance of endogenous renin in normal rats and in rats with a single ischemic kidney was investigated.

MATERIAL AND METHODS

Male Wistar rats weighing 170 to 190 g were used. Standard food and tap water were offered ad libitum, except that food was withheld for 24 hours before surgery. The animals were separated into two groups: (1) rats having ischemia of one kidney—the procedure used to produce unilateral renal ischemia has been described previously;[7] (2) normal rats—a subgroup of intact rats and a subgroup subjected to a sham operation—which were used as controls.

Acute Experiment.—After food had been withheld 24 hours, rats were anesthetized with sodium phenobarbital (35 mg/kg). Blood samples were obtained from a catheter inserted into a carotid artery, and blood was restored through a catheter placed in a femoral vein. Both kidneys were exposed through a ventral incision and a thread was passed carefully below each renal hilum. Both hili were tied at the same time and both kidneys were removed. The ventral incision was closed; and 5 minutes after the tying of the renal hili, the first blood sample was drawn. Thereafter, blood samples (0.3 ml each) were withdrawn at 15, 30, 45, 60, 90, and 120 minutes. Blood volume was kept constant by giving equal amounts of blood from donor rats nephrectomized 2 hours previously. The blood samples were collected in heparinized cooled tubes. After centrifugation, plasma was separated and the endogenous renin was measured according to the method of Nasjletti and Masson.[8]

At 24 hours after nephrectomy, we injected intravenously a dose of renin, sustained pressor principle, or a crude kidney extract prepared from

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an acetone powder of hog kidney by Hass procedure A. (Isopressor doses of these preparations release about the same amount of pressor substances when incubated under identical conditions.) The amounts recovered by serial sampling of blood were expressed as means with standard errors, and the statistical significance of differences was determined by the nonpaired *t* test.

RESULTS

The mean half-life of renin activity was defined as the time at which the initial activity was reduced to 50%. Because no differences were observed between results from intact and sham-operated rats, the two subgroups were combined, making a single normal group.

Among the 18 rats with renal ischemia, however, were 6 in which the half-life of renin activity was very prolonged; and these 6 were found to have severe renal ischemia. To prevent a falsely significant difference between experimental and control animals, the 6 experimentals with severe ischemia were separated from the 12 with mild ischemia.

Endogenous Renin.—The half-life of endogenous renin activity in normal rats (n = 23) was 31.8 ± 1.29 min, whereas in rats with renal ischemia (n = 18) it was 53.8 ± 6.83 min. The difference is statistically significant ($P<0.01$).

The half-life of renin activity in the subgroup with mild ischemia was 39.3 ± 1.81 min, which was significantly different from controls ($P<0.01$). In the subgroup with severe ischemia, the half-life of renin activity was 89.4 ± 11.5 min. The difference between this and the finding in normals is highly significant ($P<0.001$).

When the logarithm of the percentage of remaining renin activity was plotted against time, the resulting disappearance curve represented the sum of two exponentials. A straight line was fitted by the method of least squares. The results obtained are represented in Figure 1. In normal rats the mean half-life of the fast component was 11.5 minutes and that of the slower component was 67 minutes. In rats with mild renal ischemia, the fast-component half-life was 11 minutes and the slow-component half-life 84. And in the rats with severe renal ischemia, an average half-life of 8 minutes was found for the fast component and 121 minutes for the slower component.

The ratio of the calculated amounts of the two components differed among the three groups—the slower
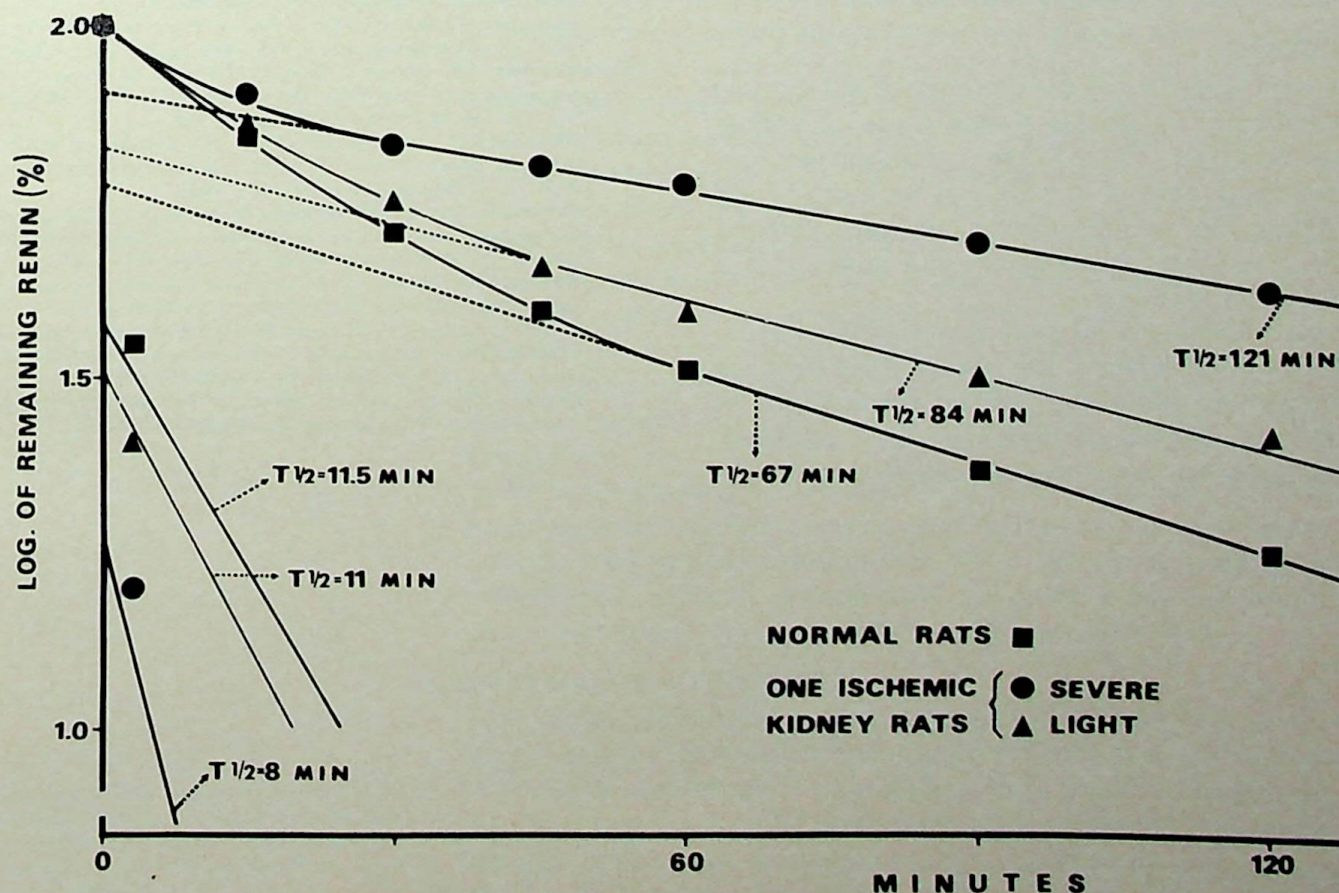
Fig. 1. Log of percentage of remaining renin activity, plotted against time. Straight lines are slopes of two components. Mean life (*T*½) of each component is indicated.

Table 1.—**Half-Life of Endogenous Renin and Exogenous Pressor Preparations in Rats, and Calculated Amount of Each Component in Different Experimental Conditions**

	Fast component		Slow component	
	Half-life, min	Amount, %	Half-life, min	Amount, %
Exogenous				
Renin	8.5	73.2	124	26.8
Sustained pressor principle	. . .	12.7	90	87.3
Crude extract	8.0	58.8	68	41.2
Endogenous renin				
Normality	11.5	39.7	67	60.3
Renal ischemia				
Mild	11.0	31.8	84	68.2
Severe	8.0	17.8	121	82.2

component being 60.3% in the normal rats, 68% in those with mild renal ischemia, and 82% in those with severe renal ischemia (Table 1).

Exogenous Pressor Substances.—The results for exogenous renin, sustained pressor principle, and crude extract were analyzed in the same way, with the results shown in Table 1. The mean half-life of the fast component of the sustained pressor principle was impossible to calculate, because the amount of the component present was too small (13%).

DISCUSSION

The present study shows the presence of at least two components in the disappearance curve of endogenous renin in rats. This is in agreement with previous observations by several investigators for humans and normal dogs. Some of the investigators have assumed that these renin components are the product of a compartmental distribution.

The experiment with exogenous preparations, however, showed that whereas the crude extract behaves like endogenous renin, the purified preparations of renin and sustained pressor principle behave predominantly as do the fast and slow components, respectively. This observation and the fact that the rats with severe renal ischemia have a greater percentage of the slower component suggest that more than one type of renin may be produced and released by the kidney.

We do not know why the slow component does not have the same half-life in the different circumstances of the experiment. One interesting possibility could be that another substance may be attached to the renin protein molecule, giving it a different half-life in the circulating blood.

It also seems that the kidney is important in the metabolism of renin. In this regard, it is important to point out the increase in the amount of the slower component, correlative with the degree of renal ischemia. If renal ischemia is known to produce hypertension, the previous observation could be important in the relation between the renin-angiotensin system and hypertension.

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The Role of Calcium in the Response of Rabbit Aorta to Angiotensin

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The role of Ca^{++} in the stimulus-contraction coupling of the response of the isolated rabbit aorta to angiotensin II was investigated. Angiotensin was found to have lower intrinsic activity than epinephrine and to be more sensitive to acute exposure of the organ to Ca^{++}-free medium. Two minutes after removal of Ca^{++}, the maximal responses to angiotensin and epinephrine were reduced by 40% ± 8% and 7% ± 5%, respectively. Further loss of response for the two agonists followed parallel time courses. In another series of experiments, angiotensin tachyphylaxis was obtained in the rabbit aorta by administration of either [1-sarcosine]angiotensin or betainyl-angiotensin. The intrinsic activity of [1-sarcosine]angiotensin was lower than that of angiotensin and was not affected by removal of Ca^{++}. It is concluded that the low intrinsic activity and the tachyphylaxis may be dependent on a strong binding of the molecule's positively charged N-terminus to sites responsible for release of Ca^{++} into the cell.

The action of substances that contract smooth muscles is thought[1] to be mediated by activation of the contractile elements by calcium ions mobilized from two sources: an extracellular pool of Ca^{++} which may be loosely bound to superficial sites on the cell membrane, and an intracellular pool of Ca^{++} tightly bound to a location that varies for different types of smooth muscle (for example, mainly plasma membrane in the guinea pig ileum, largely sarcoplasmic reticulum in the rabbit aorta[2]).

The current consensus in that mobilization of intracellular Ca^{++} produces a fast, transient (phasic) contraction, whereas transfer of extracellular Ca^{++} into the cell causes a slower, more sustained (tonic) contraction. In some arteries (for example, rabbit mesenteric and ear arteries), a bimodal response is observed, whereas in others (for example, rabbit aorta) the phasic and tonic components of the contraction are not clearly distinguishable. Nevertheless, the response of rabbit aorta to norepinephrine appears to result mainly from intracellular Ca^{++}, whereas potassium-induced contractions seem to be dependent on the extracellular pool.[3] According to van Breemen and associates,[3] in rabbit aorta angiotensin appears to release calcium from the same intracellular fraction as does norepinephrine.

We have obtained more information on the mechanism of the action of angiotensin on the rabbit aorta by studying the calcium dependence of that activity. We have also found that rabbit aorta may show angiotensin tachyphlaxis, a useful phenomenon for probing into the nature of the stimulus-contraction coupling in smooth muscles.[4]

MATERIALS AND METHODS

Contractions of isolated helical strips of rabbit aorta,[5] under 4-g loads, were recorded isometrically through a Sanborn force transducer, a Hewlett-Packard model 311A amplifier, and a Heath-Schlumberger model EU-205-11 recorder. Ca^{++}-free medium was obtained by simply omitting $CaCl_2$ from the normal salt solution. [5-Isoleucine]angiotensin II (angiotensin), [1-sarcosine, 5-isoleucine]angiotensin II ([Sar[1]]angiotensin),

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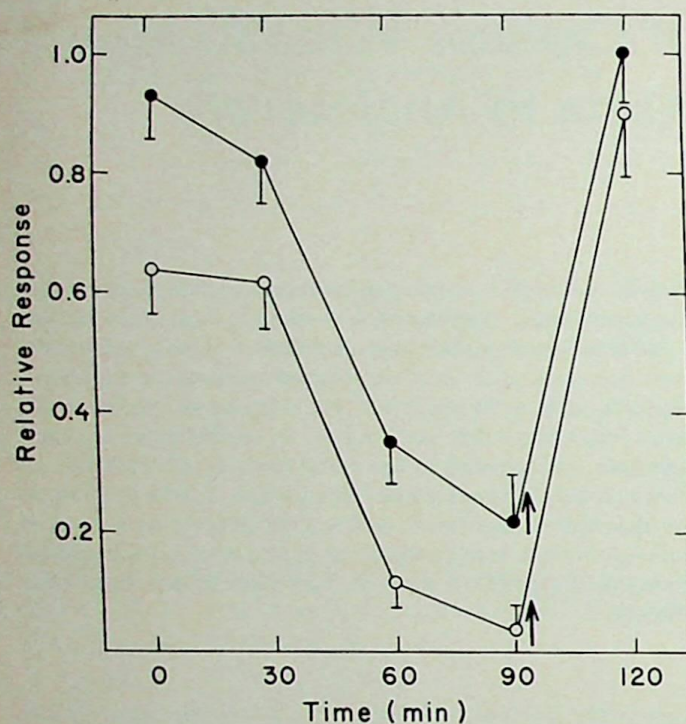
Fig. 1. Response of isolated rabbit aorta to 6.8×10^{-6} M epinephrine (filled circles) and to 1.2×10^{-7}M angiotensin (open circles). Normal medium was replaced by Ca^{++}-free medium at time zero. Responses are relative to contraction produced by same dose applied 30 minutes before Ca^{++} removal. *Arrows* indicate replacement of organs in normal Ca^{++}-containing medium. Each point is average of four to six independent experiments, and standard deviations are indicated.

and betainyl-angiotensin were synthesized in this laboratory.

RESULTS AND DISCUSSION

The maximum contraction produced by angiotensin in the rabbit aorta was about 60% of that induced by epinephrine, as previously reported.[6] A further difference between the two agonists was found in the calcium dependence of their action. Incubation in Ca^{++}-free medium for 2 minutes before addition of a maximal dose resulted in a 7% (±5) reduction in the response to epinephrine, as compared with that observed in normal medium. For angiotensin, in similar experiments, a much larger reduction (40% ± 8) occurred. When the organ was maximally contracted by epinephrine or angiotensin in Ca^{++}-free medium, addition of Ca^{++} to restore its normal concentration of 2.4 mM caused further contraction until the responses attained the level previously observed for the same preparation in normal medium. These results indicate that the response of the rabbit aorta to angiotensin is more dependent on the extracellular Ca^{++} pool than is the response to epinephrine.

The time course of the loss of response to maximal doses of the two agonists in Ca^{++}-free medium was studied, with the results shown in Figure 1. The greater Ca^{++} dependence of the angiotensin response was evident after 2 minutes in the Ca^{++}-free medium, but subsequent loss of response to the two agonists followed approximately parallel kinetic courses.

Our results suggest that a significant fraction of the effect of angiotensin is mediated by external or loosely bound Ca^{++} that is distinct from the tightly bound source mobilized by epinephrine. The parallel loss of response to the two agonists in Ca^{++}-free medium indicates either of the two following possibilities: (1) part of the effect of angiotensin is a result of release of Ca^{++} from the same pool drawn on by epinephrine; (2) a slow equilibrium (more than 2 minutes, less than 30 minutes) is established between the tightly bound Ca^{++} (mobilized by epinephrine) and the angiotensin-sensitive Ca^{++} pool. The second hypothesis appears more plausible because it might explain the inability of angiotensin to produce total response of rabbit aorta, in contrast to the full activity of epinephrine. If both agonists acted on the same Ca^{++} source, the lower intrinsic activity of angiotensin would have to be ascribed either to a smaller number of angiotensin receptors or to a less efficient drug-receptor complex, in spite of the fact that the activity of angiotensin is manifest in molar concentrations one order of magnitude lower than is the case with epinephrine. If a more superficial Ca^{++} pool were mobilized by angiotensin, the lower intrinsic activity might be explained by a less efficient release of Ca^{++} into the cell, resulting in lower steady-state intracellular concentrations and, consequently, lower intrinsic activity.

An explanation of the reason for the lower efficiency of the release of Ca^{++} by angiotensin may be obtainable from an analysis of the tachyphylactic phenomenon. The specific acute desensitization to angiotensin (tachyphylaxis), common in other smooth muscles,[7] is not evident in rabbit aorta.[7,8] However, because it was shown that angiotensin tachyphylaxis in rat uterus and guinea pig ileum is dependent on the protonated amino group of the peptide,[9] we have investigated the possibility that analogues with more basic N-terminal groups might induce tachyphylaxis in the rabbit aorta. We have found that [Sar[1]]angiotensin is strongly tachyphylactic in that organ, in agreement with recently published independent observations.[10] Furthermore, we have also found that the rabbit aorta rendered tachyphylactic to [Sar[1]] angiotensin is also specifically unresponsive to
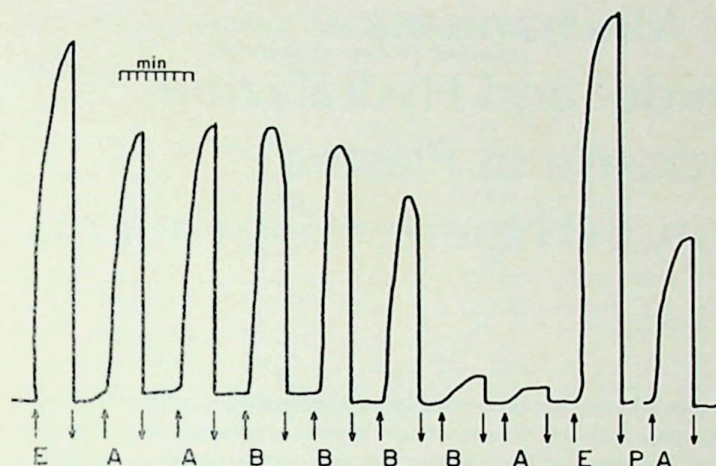
Fig. 2. Response of isolated rabbit aorta to maximal doses of epinephrine (*E*; 6.8×10^{-6} M); angiotensin (*A*; $1.2 < 10^{-7}$ M); and betainyl-angiotensin (*B*; 2×10^{-7}M). *Upward arrows* = additions to muscle bath; *downward arrows* = washes with fresh medium and interruption of chart movement. Interval between additions, 30 minutes. At *P*, recording was interrupted while preparation rested for 2 hours.

angiotensin and that this phenomenon is reversible. Similar results, including the cross-tachyphylaxis to angiotensin, were obtained with betainyl-angiotensin, and results of a typical experiment are shown in Figure 2. This indicates that in rabbit aorta, as in other smooth muscles,[9,11] the positive charge in the N-terminus of the molecule is important for the manifestation of tachyphylaxis.

It is interesting to note that we found the intrinsic activity of [Sar¹]angiotensin to be even lower than that

Table 1.—**Intrinsic Activities* in Isolated Rabbit Aorta**

Agonist	Ca^{++} concentration	
	2.4 mM	0†
Epinephrine	1.00	0.93
Angiotensin	0.64	0.38
[Sar¹]angiotensin	0.38	0.37

*Relative to the maximum response to epinephrine obtained in medium containing 2.4 mM of Ca^{++}.
†Assayed 2 minutes after replacing normal medium by Ca^{++}-free medium.

of angiotensin and that this activity did not seem to be affected by loosely bound Ca^{++} (Table 1).

Our interpretation of these findings is that the low intrinsic activity of [Sar¹]angiotensin may result from strong binding of the molecule (through its N-terminus) to sites responsible for the release of Ca^{++} into the cell. This would lower the efficiency of the response to external Ca^{++} and also might explain tachyphylaxis. One is also tempted to speculate that a similar mechanism might be involved in the action of angiotensin, although to a smaller degree. Thus, the lower intrinsic activity of angiotensin might be conceived as a tachyphylactic manifestation which is evident in the rabbit aorta because of the slowness of that organ's response in comparison with other smooth muscles.

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Physiologic Mechanisms of Bupicomide- and Hydralazine-Induced Increase in Plasma Renin Activity in Hypertensive Patients

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A study was made of the possible mechanisms underlying bupicomide- and hydralazine-induced increase of plasma renin activity. Six patients with mild to moderate hypertension were treated with both bupicomide and hydralazine on separate occasions in random order. Bupicomide lowered mean arterial pressure from 124.2 ± 3.7 mm Hg (mean ± SE) to 107.2 ± 3.9 mm Hg ($P < 0.001$). The associated increase in plasma renin activity was 1.27 ng/ml per hour and the increase in heart rate was 16.5 beats/min. Hydralazine reduced mean arterial pressure from 124.2 ± 3.7 mm Hg to 107.0 ± 2.0 mm Hg ($P<0.01$). The associated increase in plasma renin activity was 2.20 ng/ml per hour and the increase in heart rate was 22.4 beats/min. Plasma renin activity during bupicomide and hydralazine administration correlated positively with control plasma renin activity ($r = 0.98$, $P < 0.001$). The log of plasma renin activity correlated positively with heart rate ($r = 0.51$, $P < 0.02$) and negatively with mean arterial pressure ($r = -0.62$, $P < 0.005$). We conclude that control plasma renin activity is a major determinant of change in plasma renin activity during administration of bupicomide or hydralazine. Both an increase in sympathetic activity and a decrease in perfusion pressure may contribute to the bupicomide- and hydralazine-induced increase in plasma renin activity, possibly by a baroreceptor-mediated increase in adrenergic tone.

Vasodilator antihypertensive agents such as hydralazine[1] and minoxidil[2,3] often are used in combination with beta blockers in the treatment of arterial hypertension. Beta blockers such as propranolol[4] counteract appropriate manifestations of the increase in sympathetic tone induced by vasodilators. An additional hypotensive effect of propranolol in patients treated with minoxidil has been attributed in part to a decrease in cardiac output. In addition, suppression of plasma renin activity may contribute to the decrease in arterial pressure. Several vasodilator antihypertensive drugs, such as hydralazine,[5] minoxidil,[5] and diazoxide,[6] have been shown to increase the plasma renin activity. This increment in plasma renin activity may be caused by at least three mechanisms—an increase in adrenergic tone, a decrease in arterial pressure, or a decrease in urinary sodium excretion rate.

In this study we report evidence about the underlying mechanisms of the increase in plasma renin activity induced by hydralazine and a recently available vasodilator antihypertensive agent, bupicomide. Bupicomide[7] has been reported to decrease arterial pressure in patients with essential hypertension. The systemic hemodynamic effects of bupicomide are similar to those of hydralazine.[7]

MATERIAL AND METHODS

Six patients with mild to moderate hypertension were studied in a metabolic ward. The clinical data are shown in Table 1. The ages of the patients ranged between 20 and 54 years. Cardiac status was normal in

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Table 1.—**Clinical Data for Patients Treated With Bupicomide and Hydralazine**

Patient	Age (yr), sex	Weight, kg	Blood urea nitrogen, mg/dl	Creatinine clearance, ml/min	Hypertensive retinopathy*
1	41, F	74.8	9	99	0
2	40, F	66.0	13	81	I
3	54, F	105.0	8	84	I
4	42, F	77.7	10	82	I
5	35, M	81.2	19	47	II
6	20, M	81.2	10	109	I

*Funduscopic grades of Keith-Wagener.

each patient. Renal function was normal except in one patient. In only one patient was hypertensive retinopathy greater than Keith-Wagener grade I. In each case informed consent for study was obtained.

Dietary sodium was constant at 100 meq/day. Arterial pressure and heart rate were determined in duplicate every 3 hours with the patient in the recumbent position. Mean arterial pressure was calculated as diastolic pressure plus one-third pulse pressure. About 3 days were allowed for stabilization of weight and arterial pressure, after which the first placebo period was begun. Drugs were administered every 6 hours in randomized order. The drug periods were separated by a second placebo period of 7 days. Bupicomide was given in oral doses ranging from 900 mg to 2,000 mg per day, and hydralazine in oral doses ranging from 300 mg to 600 mg per day.

Plasma renin activity was determined with the patient in the upright position at noon after 1 hour of ambulation. Plasma renin activity was measured by a modification of the radioimmunoassay of generated angiotensin I, using an incubation of 3 hours at a pH of 7.4.[8] Statistical comparisons were performed by paired *t* test. Regression analysis was performed by least squares.

RESULTS

Table 2 shows the mean arterial pressure, heart rate, plasma renin activity, and urinary sodium excretion rate during placebo, bupicomide, and hydralazine periods. No statistical differences were observed between placebo periods 1 and 2 for any of these
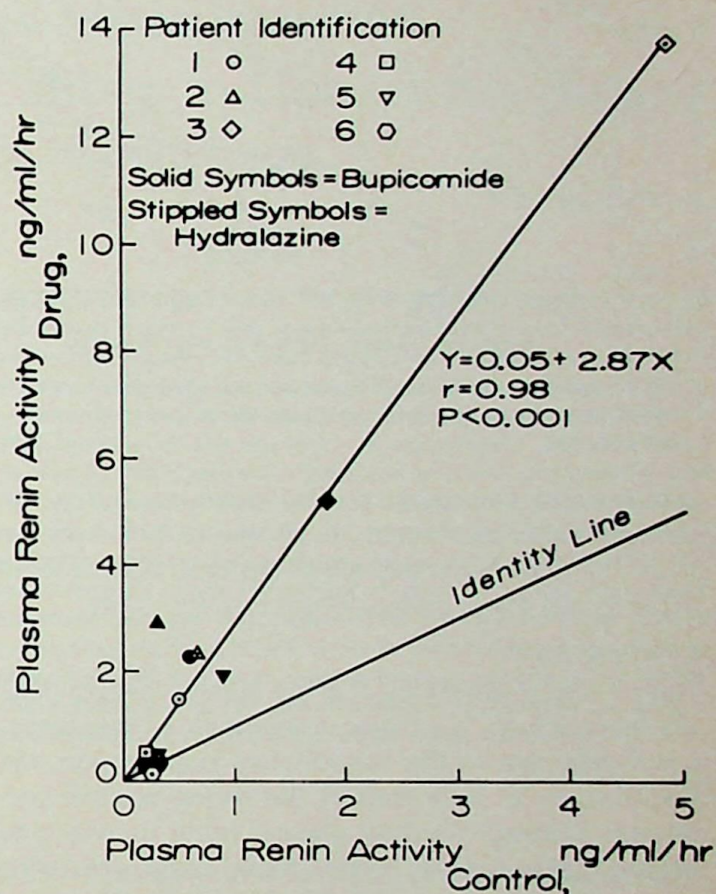
Fig. 1. Relationship of control plasma renin activity to plasma renin activity during administration of bupicomide and hydralazine.

factors. During the administration of each drug, recumbent mean arterial pressure was reduced to the same absolute level. Each drug induced a significant increase in heart rate, and bupicomide a significant increase of plasma renin activity.

Figure 1 illustrates the relationship of control plasma renin activity to plasma renin activity during the administration of bupicomide and hydralazine. There was a positive correlation ($r = 0.98$, $P<0.001$) between these findings. Figure 2 illustrates a positive correlation ($r = 0.51$, $P<0.02$) between the log of plasma renin activity and the heart rate during the administration of placebo, bupicomide, and hydralazine. There was also an inverse correlation ($r = -0.62$, $P<0.005$) between the log of plasma renin

Table 2.—**Results of Placebo and Drug Administration (Mean ± SE)**

Protocol period	Mean arterial pressure, mm Hg	Heart rate, beats/min	Plasma renin activity, ng/ml per hour	Urinary sodium excretion rate, meq/24 hours
Placebo 1	126.3 ± 3.35	73.8 ± 4.30	0.67 ± 0.25	73.1 ± 23.4
Placebo 2	122.0 ± 4.02	75.8 ± 4.17	1.12 ± 0.73	71.4 ± 15.7
Bupicomide	107.2 ± 3.85*	91.3 ± 3.66*	2.17 ± 0.74†	102.3 ± 15.5
Hydralazine	107.0 ± 1.99‡	97.2 ± 5.78*	3.10 ± 2.17	75.6 ± 19.7

Significance of difference from placebo P^+ (mean of P_1 and P_2): *$P<0.001$; †$P<0.05$; ‡$P<0.01$.
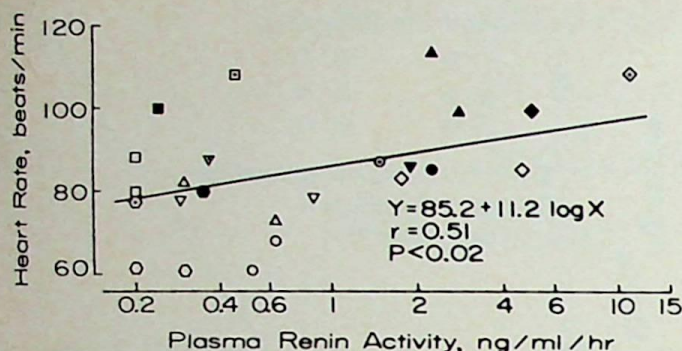
Fig 2. Relationship between log of plasma renin activity and heart rate during administration of placebo, bupicomide, and hydralazine.

activity and the mean arterial pressure during the administration of placebo, bupicomide, and hydralazine. No correlation was found between plasma renin activity and the urinary sodium excretion rate.

DISCUSSION

The present study shows that the control level of plasma renin activity is a major determinant of the plasma renin response to the vasodilators bupicomide and hydralazine, as indicated by the strong positive correlation between control plasma renin activity and plasma renin activity while these drugs are being taken. There was no apparent difference in this correlation as a function of bupicomide versus hydralazine.

In man, a number of procedures that increase sympathetic nervous activity are associated with increased plasma renin activity. Thus, Gordon and associates[9] demonstrated that upright posture and exposure to cold provoke increases in urinary catecholamines and plasma renin activity. Furthermore, Esler and Nestel[10] demonstrated a positive correlation between changes in plasma renin activity and urinary norepinephrine excretion in response to head-up tilting.

In the present study, a positive correlation was found between heart rate and log of plasma renin activity during administration of bupicomide and hydralazine. This observation is in keeping with the study of O'Malley and associates[11] and that of Ueda and associates,[12] who demonstrated that changes in heart rate and plasma renin activity induced by minoxidil and hydralazine, respectively, were positively correlated. It is interesting that mean blood pressure correlated negatively with plasma renin activity, which may indicate that increases in heart rate and plasma renin activity caused by bupicomide or hydralazine were secondary to a reflex mechanism in response to peripheral vasodilation. It is unlikely that sodium balance played an important role in the increase of plasma renin activity, because in our study urinary sodium excretion rate did not correlate with plasma renin activity.

We conclude that control plasma renin activity is a major determinant of bupicomide- and hydralazine-induced increase in plasma renin activity. Changes in both the sympathetic nervous system and perfusion pressure may contribute to the effect, possibly by a baroreceptor-mediated increase in adrenergic tone.

ACKNOWLEDGMENT

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Continuous Measurement of Aortic Caliber in Conscious Rats
Effect of Acute Hypertension

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For continuously measuring the circumference of the aorta in conscious rats for up to 20 days, a new electrolytic strain gauge of high sensitivity and stability was constructed of silicone tubing filled with copper nitrate. The mean systolic and diastolic circumferences measured in 11 nonanesthetized undisturbed rats were 6.557 ± 0.128 mm and 6.533 ± 0.128 mm, respectively—the pulse pressure (51 mm Hg) producing an increase of 0.024 mm in aortic size (0.37% increase of the diastolic circumference). The calculated dynamic elastic modulus was 13,908 dynes/cm². Infusions of blood, angiotensin, and noradrenaline to increase mean aortic pressure acutely by 50 mm Hg caused aortic circumference to increase by 0.59, 0.58, and 0.53%, respectively. Seven rats were subjected to acute hypertension produced by subdiaphragmatic aortic constriction after recording the control measurements. Over the period of study (6 hours) after aortic constriction, mean aortic blood pressure was increased 50 mm Hg from the control of 101 mm Hg. A mean maximal increase of 6% in aortic circumference was seen at 3 hours and a mean minimum of 0.9% at 4 hours, with an average increase of 3% for the entire 6-hour period. These changes in aortic circumference coincide with an upward displacement of about 30% in the range of activation of the aortic baroreceptors.

The time course of the baroreceptor resetting in acute hypertension in the rat was studied by recording the afferent neural activity in the aortic depressor nerves[1] and analyzing the heart rate changes in conscious undisturbed animals.[2] Both studies showed that the process of adaptation is progressive and that complete adaptation occurs after 1 to 2 days of hypertension. It has been suggested that the resetting of the baroreceptors is caused by alteration in the aortic wall properties secondary to hypertension, rather than by receptor changes.[3-6] However, these studies were performed by comparing animals already hypertensive with normotensive controls. The purpose of the present experiment is to analyze the changes in aortic circumference in the same animals before and during the early phases of acute hypertension when the process of resetting is developing, using a method with sufficient sensitivity and stability to permit measuring the aortic caliber continuously in conscious rats.

MATERIALS AND METHODS

An electrolytic strain gauge for implantation in the descending aorta of rats (about 6.50 mm of circumference in male Wistar rats weighing 200 to 230 g) was constructed of silicone tubing (medical grade tubing 602-106, Dow Corning Corporation) of 0.64 mm outside diameter and 0.30 mm inside diameter, with a total length of 60 mm, filled with a solution of copper nitrate (60% saturated). Nickel-chrome wires (0.1-mm diameter) were fitted into the silicone tubing in such a way that the inter-electrode distance was about 3.50 mm and the total cell length was 6.00 to 6.50 mm. Distention of the strain gauge produced a decrease in cross-sectional area with no change in volume and an increase in
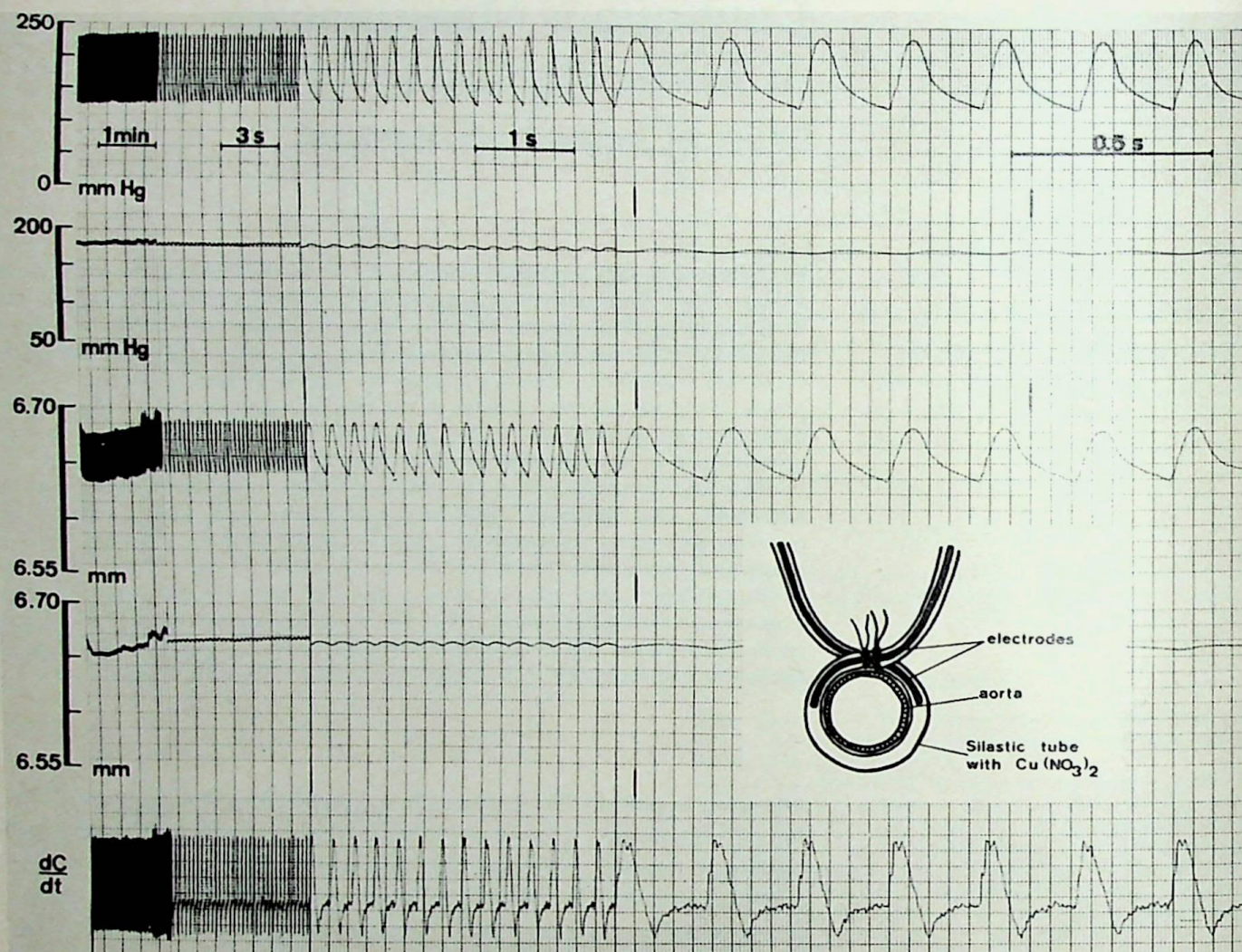
Fig. 1. Simultaneous recording of pulsatile and mean aortic blood pressure (*top*), aortic circumference (*middle*), and rate of change in circumference (*bottom*) in the conscious rat 6 hours after subdiaphragmatic aortic constriction. *Inset:* electrolytic transducer placed around aorta.

electrical resistance. The electrolytic strain gauge was connected to a Wheatstone bridge built with appropriate resistances. Electrical excitation of the system (5 V, 25 kHz) was supplied by a Tektronix 3C66 preamplifier. Calibration of the strain gauge was performed by measuring the changes in resistance produced by progressive (0.2-mm) elongation of the silicone tubing under a microscope (Zeiss 350 882). Calibration was adjusted to the body temperature of the rat because the electrolytic conductivity of the device is affected by temperature.

The descending aorta was exposed through a lateral thoracotomy (third left intercostal space) performed under pentobarbital anesthesia and positive pressure artificial respiration. The strain gauge was implanted around the vessel (according to the diagram seen in Figure 1), and its length was adjusted to maintain a distention of 5% of the resting length of the tubing. Four days after implantation, and with ether anesthesia, the strain gauge ends were exteriorized and connected to a miniature socket fixed on the skull with a fast-polymerizing methacrylate. Blood pressure was measured by means of a plastic cannula (PE 10 connected to a PE 50) inserted into the ascending aorta through the left carotid artery. The strain gauge and the arterial cannula were connected to a polygraph (Hewlett-Packard 7848A) to permit continuous measurement without disturbing the spontaneous motor activity of the rat. The rate of change of the aortic circumference (dC/dt) was measured by a derivative computer (8814A, Hewlett-Packard). To produce acute hypertension, the rats were subjected to subdiaphragmatic aortic constriction under ether anesthesia according to the technique described previously.[1]

RESULTS AND DISCUSSION

Aortic size is given in circumference values (instead of diameter) because it was obtained thus. Simul-
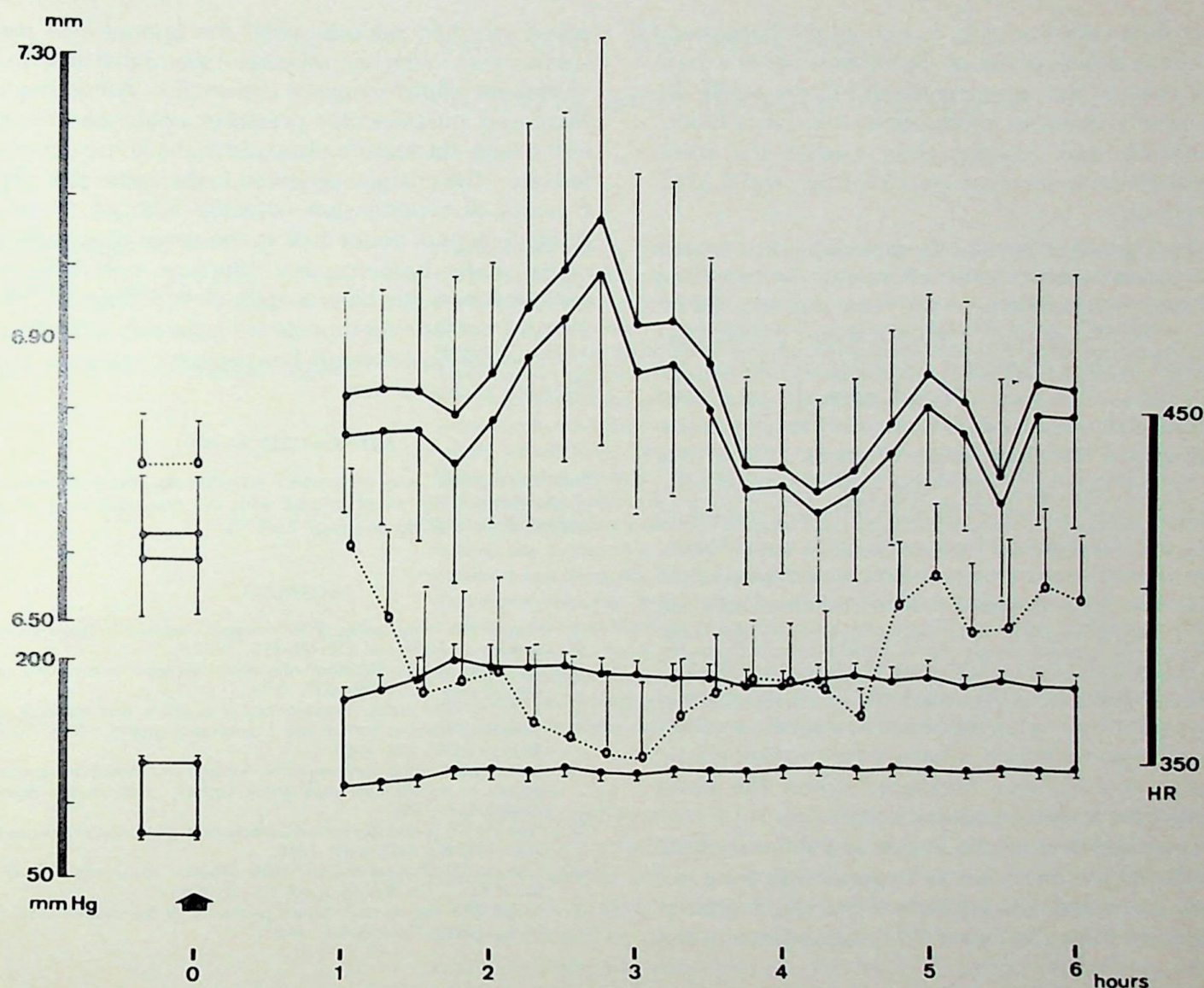
Fig. 2. Alterations in systolic and diastolic circumferences of the aorta (*top*), heart rate (o · · · o, scale right), and blood pressure (*bottom*) produced by subdiaphragmatic aortic constriction (*arrow*). Values are means ± SE for a group of seven rats.

taneous recordings of intra-aortic pressure and wall circumference (Fig. 1) yielded almost identical curves, indicating the great sensitivity of the method used for measuring aortic size. Aortic circumference increased as systolic pressure increased, and reached its maximum simultaneously with the peak pressure. Both returned gradually to the diastolic levels. The measurements were repeated every day for periods up to 10 days in nine rats. In six of these animals the values for aortic circumference remained stable; but in the other three a sudden increase in the resistance occurred, indicating damage of the electrolytic strain gauge (air bubbles in the tubing).

Control measurements were obtained from another group of 11 conscious Wistar rats (weighing 200 to 230 g) 4 days after the implantation of the devices. The systolic and diastolic pressures were 128 ± 3 and 77 ± 3 mm Hg, respectively; heart rate was 408 ± 9 beats/min; and systolic and diastolic circumferences were 6.557 ± 0.128 mm and 6.533 ± 0.128 mm, respectively. The pulse pressure of 51 mm Hg produced a 0.024-mm (0.37%) increase in aortic circumference. The strain caused by the pressure pulse on the aorta of the rat is consequently smaller than the 0.8% and 1.0% observed in the rabbit[3] and the dog,[6] respectively. The dynamic elastic modulus in the control rats, calculated as proposed by Peterson and associates[5] with use of circumference instead of diameter ($Ep = \frac{\Delta P \times C}{\Delta C}$), was 13,908 dynes/cm^2, a value higher than that reported for the aorta of dogs and rabbits.[3] The high dynamic stiffness exhibited

by the aorta could be due, in part, to the faster heart rate[7] characteristic of the rat. Another series of experiments showed that an increase of 50 mm Hg in the mean arterial pressure, produced by infusion of blood, angiotensin, and noradrenaline, caused the aortic circumference to increase by 0.59, 0.58, and 0.53%, respectively.

A third group of seven rats were subjected to subdiaphragmatic aortic constriction after the recording of control measurements. One hour was allowed for recovery of the animals. Figure 2 shows the changes observed in the continuous recording for periods up to 6 hours. The mean blood pressure increased immediately from a control value of 101 mm Hg (mean pressure) and remained stable at about 150 mm Hg (140 to 158 mm Hg). The heart rate decreased from a control value of 435 ± 14 beats/min to a minimum of 353 ± 21 beats/min 3 hours after aortic constriction. The mean aortic circumference increased an average of 3.02% for the entire period, with a maximal increase of 6.3% after 2 hours 45 min and a minimum of 0.94% after 4 hours 15 min. The largest value of dynamic elastic modulus (14,490 versus 9,333 in the control period) was observed simultaneously with the smallest increase in aortic length, whereas the smallest elastic modulus (6,520) was measured when the aorta exhibited the largest increase in size.

The marked fluctuations in size and stiffness of the aorta during the first hours of hypertension were not directly correlated with equivalent changes in arterial pressure, as shown in Figure 2. Because three of the seven rats had periods when the arterial size was smaller than in the control state, it seems that an active vasoconstriction (myogenic constriction in response to increased intravascular pressure) could contribute to the large fluctuation observed in the aortic circumference. The changes observed in the aortic size after 6 hours of hypertension coincide with an upward displacement of about 30% in the range of activation of the aortic baroreceptors. Because complete resetting of the aortic baroreceptor takes place after only 2 days,[1] further experiments are necessary to analyze the correlation between baroreceptor resetting and changes in aortic size.

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Vascular Renin-Like Activity and Blood Pressure

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Plasma renin activity, renin-like activity present at the artery wall, pressor response to exogenous hog renin, renin half-life time, and renin-like activity present at the artery wall 1 hour after injection of renin were measured in conscious rats 1 month after inducing hypertension by renal artery constriction and contralateral nephrectomy (one-kidney hypertension). Plasma renin activity was higher but without statistical significance in one-kidney hypertensive rats when compared with normotensive or sham-operated animals. Renin-like activity present at the artery wall was significantly increased in hypertensive animals only when compared with one-kidney normotensive rats. Pressor responses to renin in one-kidney hypertensive and normotensive rats were of significantly longer duration than in sham-operated animals. The inactivation rate of exogenous renin followed a first-order reaction with a half-life of 6 minutes in sham-operated rats and of 12 minutes in one-kidney hypertensive and normotensive animals. Decreased inactivation of circulating renin could explain the protraction of the pressor response; however, the slope of the regression equation describing the inactivation of renin in all of the rats was steeper than the slope of the pressor response, indicating a dissociation between blood pressure and plasma renin activity. The renin-like activity present at the artery wall 1 hour after injection of renin was determined in the three groups; the arterial tissue of one-kidney hypertensive rats bound more circulating renin than that of normotensive rats and the latter more than that of sham-operated animals, suggesting the participation of this binding capacity in the protraction of the pressor response and in the maintenance of hypertension.

The role played by renin in the initiation and maintenance of renovascular hypertension remains obscure. Experimental models have been widely studied in the rat and in the dog without arriving at definitive conclusions. Different mechanisms seem to be involved in the development of hypertension caused by renal artery stenosis in the presence and in the absence of a contralaterally intact kidney. We have observed, in renal hypertensive dogs that have renal artery stenosis in the presence of an intact contralateral kidney, that nephrectomy of the latter reduces plasma renin activity to normal values, whereas blood pressure climbs to higher levels.[1] Moreover, in rats with unilateral renal artery stenosis and contralateral nephrectomy (one-kidney hypertensive rats), plasma renin activity is very high in some animals and normal or below normal in others, without correlation with the blood pressure.[2]

The possibility that circulating renin could be more easily bound to the artery wall or that the renin-like enzyme of the blood vessels could play some role in maintaining high blood pressure in this type of hypertension has not been investigated. In previous studies performed in our laboratory, we found an increased magnitude and a protracted pressor response to renin in renal hypertensive rats with renal artery constriction and contralateral nephrectomy.[3] Other authors have described a similar potentiation.[4] In view of our findings in bilaterally nephrectomized rats, the potentiation of the renin response could be caused by a significant increase in renin half-life time or by enhanced and prolonged binding of the enzyme to the artery wall, or both.[5] Some authors, by using antisera to angiotensin II, have shown indirectly that in one-kidney renal hypertensive rats

angiotensin could be formed at the vascular wall in a location that is not accessible to large circulating antibody molecules and in a quantity large enough to occupy most of the specific receptors.[6]

Direct investigation of the behavior of the renin-angiotensin system at the vascular wall is lacking. Thus, we designed the present experiment to study the following in one-kidney hypertensive rats: (1) plasma renin activity and the amount of renin present at the artery wall, (2) the pressor effect of exogenous renin, (3) the half-life of exogenous renin, and (4) the amount of renin present at the arterial wall 1 hour after the renin injection.

MATERIAL AND METHODS

We used male rats of the Wistar albino strain in the weight range of 200 to 300 g. Unilateral nephrectomy of the right kidney was performed in 60 animals; hypertension was induced in 38 of them by placing a silver clip on the left renal artery; a sham operation was conducted in the remaining 22 rats. In the clip-operated group, 3 rats died during the first week, 25 developed hypertension (blood pressure above 150 mm Hg sustained for more than 2 weeks), and 10 remained normotensive. We shall refer to one-kidney normotensive and one-kidney hypertensive rats in the following discussion.

The animals were weighed and their blood pressure was measured by the indirect plethysmographic tail method each week. Four weeks after the surgical procedures, in all the animals an indwelling Silastic cannula was placed in the jugular vein and a loose ligature was placed around the hilum of the remaining kidney through a lumbar incision; both ends of the ligature were left under the skin. In seven sham-operated, four one-kidney normotensive, and seven one-kidney hypertensive rats, an indwelling Silastic cannula was also placed in the carotid artery. Both cannulas were brought through the skin at the back of the neck. Three days after this operation, the ends of the ligature were brought through the skin by gently opening the lumbar wound, and the animals were left unrestrained in a metal box for 1 hour.

In those animals that had a carotid cannula, pressor response to renin was determined. Mean arterial pressure was measured in the unrestrained unanesthetized rats through the carotid cannula. A slow infusion (20 μl/min) of 5% glucose with heparin (0.1 mg/ml) was maintained during pressure recording. A Statham P23 pressure transducer connected to a Grass polygraph was used; the transducer was calibrated against a mercury manometer just before each experiment. During the recording of the control blood pressure, a blood sample was obtained from the jugular vein (100 μl). Renin (0.2 GU, purified hog renin from General Biochemicals) was injected through the same cannula and the cannula was flushed out with 0.05 ml of a 5% dextrose solution. Blood samples were obtained sequentially at 5, 15, 30, and 60 minutes. The kidney ligature was tightened and the animals were killed by decapitation immediately after the last blood sampling. The aorta was excised from the aortic arch to the femoral arteries, including the renal arteries and the mesenteric artery with all its finest branches. The tissue was weighed and kept frozen until assayed. In all the remaining animals only one control blood sample was obtained before they were killed.

Renin Activity Determination.—Renin-like activity present in the arterial wall and plasma renin activity were determined by radioimmunoassay of angiotensin I (Schwartz-Mann).[7] Plasma samples were kept frozen until the assay. The arterial tissue was homogenized with 10 volumes of saline containing 1.4 mg/ml of ethylenediaminetetraacetate. After centrifugation, an aliquot of the supernatant was incubated with the same volume of a pool of plasma obtained from 24-hour nephrectomized rats in the presence of the buffer and inhibitors. The results are expressed as nanograms of angiotensin I per gram per hour for arterial tissue,

Table 1.—**Comparison of Factors Among Groups of Rats**

Groups	No.	Factor, mean ± SEM: Body weight, g	Blood pressure, mm Hg	Arterial tissue weight, mg	AW:BW,* mg/g
Sham-operated rats	22	287.5 ± 6.9	116 ± 3	263.8 ± 22.9	0.90 ± 0.06
One-kidney normotensive rats	10	251.1 ± 10.5	115 ± 6	257.4 ± 34.5	1.01 ± 0.11
P_1†		<0.01			
One-kidney hypertensive rats	25	251.0 ± 7.6	162 ± 5	336.4 ± 19.2	1.34 ± 0.06
P_1†		<0.005	<0.001	<0.02	<0.001
P_2†				<0.05	<0.02

*Relation between arterial tissue weight (AW) and body weight (BW).
†P_1 = statistical difference when compared with sham-operated rats; P_2 = statistical difference when compared with one-kidney normotensive rats.

Table 2.—**Comparison of Plasma Renin Activity Among Groups of Rats**

Groups	No.	Plasma renin activity, mean ± SEM*
Sham-operated rats	22	6.81 ± 0.99
One-kidney normotensive rats	10	6.41 ± 1.33
One-kidney hypertensive rats	25	15.09 ± 4.01

*In nanograms of angiotensin I per milliliter per hour.

and as nanograms of angiotensin I per milliliter per hour for plasma.

RESULTS

Body weight, blood pressure, arterial tissue weight, and the relation of artery weight to body weight are presented in Table 1. Clip-operated rats had a significantly slower growth rate than did sham-operated animals. The arterial tissue obtained from one-kidney hypertensive rats was significantly heavier than that from one-kidney normotensive or sham-operated animals.

Plasma Renin Activity. Plasma renin activity values for the three groups studied are presented in Table 2. Some hypertensive rats had very high levels of plasma renin activity, whereas others had normal or slightly lower than normal values. The mean value for one-kidney hypertensive rats was higher than that for one-kidney normotensive or sham-operated rats; however, the difference was not statistically significant.

Renin-Like Activity of the Arterial Wall.—In Table 3, data from the rats of each experimental group have been divided according to final treatment, as follows: group 1, untreated rats, and group 2, rats injected with 0.2 GU of purified hog renin (measured 1 hour after injection).

In animals belonging to group 1, one-kidney hypertensive rats had higher values of renin-like activity of the artery wall; however, the difference was significant only when compared with one-kidney normotensive rats ($P<0.05$). One hour after renin injection, all the animals had increased amounts of renin in the arterial wall. In one-kidney hypertensive and normotensive rats, the difference was significant when compared with that in untreated rats. One-kidney hypertensive rats belonging to group 2 had the highest value of all the animals, and this value was significantly greater than those of sham-operated and one-kidney normotensive rats 1 hour after renin injection.

Pressor Responses to Renin.—Pressor responses were similar both in magnitude and in duration in one-kidney hypertensive and normotensive rats. Thus all the results are presented together, under the designation of clip-operated rats. Pressor responses to 0.2 GU of renin ranged from 25 to 80 mm Hg and lasted from 20 minutes to over 60 minutes in the clip-operated animals. In 14 of 18 animals, blood pressure had not returned to control levels when the experiment ended. In sham-operated rats, the pressor response to the same amount of enzyme ranged from 35 to 48 mm Hg and lasted less than 1 hour in 7 of 12 rats. The duration of the response in this group ranged from 5 minutes to over 1 hour. In the clip-operated rats, the pressor response was still prominent 60 minutes after renin injection, whereas in sham-operated animals blood pressure did not differ significantly from control values 30 minutes after renin injection. When both experimental groups are compared, pressor responses of clip-operated rats were significantly greater than those of sham-operated animals at 5, 10, 15, 20, 30, and 60 minutes (Table 4).

Renin Half-Life.—The rate of disappearance of exogenous injected hog renin from the plasma of clip-operated and sham-operated rats is presented in Table 5 and has been expressed as plasma renin activity in nanograms of angiotensin I per milliliter per hour.

Table 3.—**Comparison of Renin-Like Activity of the Arterial Walls* Among Groups of Rats**

Groups	No.	Activity,* mean ± SEM	P_1†	P_2†	P_3†	P_4†
Sham-operated rats						
Group 1	15	20.43 ± 5.50				
Group 2	7	28.20 ± 4.05	NS			
One-kidney normotensive rats						
Group 1	6	11.20 ± 2.31				
Group 2	4	44.68 ± 0.45	<0.001	<0.02		
One-kidney hypertensive rats						
Group 1	18	26.29 ± 6.29			<0.05	
Group 2	7	195.73 ± 64.75	<0.02	<0.05		<0.05

*In nanograms of angiotensin I per gram per hour.
†P_1 = statistical difference between groups 1 and 2 for each type of experimental animal; P_2 = statistical difference when compared with group 2 of sham-operated rats; P_3 = statistical difference when compared with group 1 of one-kidney normotensive rats; P_4 = statistical difference when compared with group 2 of one-kidney normotensive rats.

Table 4.—**Pressor Response to 0.2 GU of Purified Hog Renin in Groups of Rats***

Minutes	Sham-operated rats, mean ± SEM (N = 7)	Clip-operated rats, mean ± SEM (N = 11)
2	46.73 ± 2.72	51.83 ± 3.28
5	29.18 ± 2.21	39.50 ± 2.88
10	16.54 ± 3.88	29.67 ± 2.37
15	13.71 ± 3.61	27.17 ± 2.53
20	12.18 ± 2.89	22.56 ± 2.78
30	8.55 ± 3.12	18.00 ± 2.76
40	6.54 ± 2.83	14.27 ± 2.78
50	5.37 ± 2.68	12.55 ± 2.64
60	2.10 ± 2.27	12.39 ± 2.80

*All figures indicate blood pressure in mm Hg.

When expressed in this way, plasma renin activity was higher in clip-operated animals after renin injection, probably because of some kinetic difference that has not been investigated in present experiments. Renin half-life in sham-operated rats, calculated from the disappearance curve (Fig. 1), was 6 minutes and in clip-operated animals it was 12 minutes (Fig. 2). Plasma renin activity values after renin injection were similar in normotensive and hypertensive clip-operated rats; thus, as in the case of the pressor responses, they have been included in the same group.

Comparison Between Pressor Response and Disappearance Rate of Renin.—Plotting the pressor response and the disappearance rate of exogenous injected hog renin as a function of time in sham-operated (Fig. 1) and in clip-operated (Fig. 2) rats shows that the slope of the regression line derived from the equation describing inactivation rate was steeper than that describing pressor response. In normal animals, the decay of the pressor response was slightly steeper than that of the inactivation rate of renin.[8]

DISCUSSION

The present experiments have shown that one-kidney hypertensive and normotensive rats gained less weight than sham-operated animals. The slower growth rate most probably is a result of renal insufficiency in the clip-operated animals. On the other hand, the absolute and relative weight of the arterial tissue was
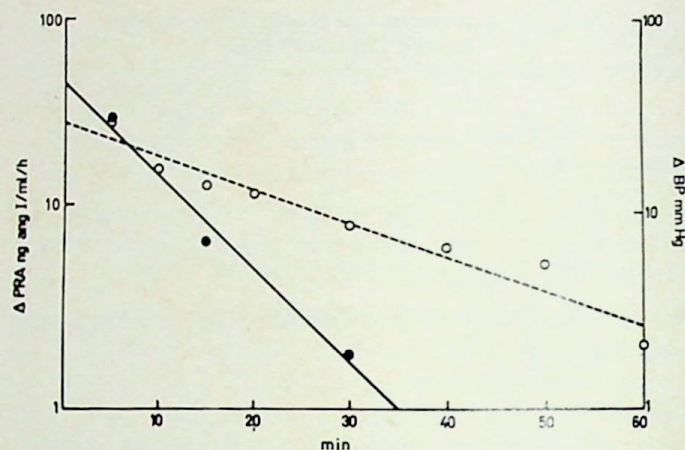
Fig. 1. Plasma renin activity and pressor response to renin at various intervals after injecting purified hog renin in sham-operated animals. Regression lines for plasma renin activity (*PRA*; solid line, solid dots) and for pressor response to renin (*BP*; broken line, open dots). Ordinates: left—plasma renin activity in nanograms of angiotensin I per milliliter of plasma per hour; right—pressor response in mm Hg. Abscissa: time in minutes.

significantly increased only in one-kidney hypertensive rats, indicating that this change could be related to the level of blood pressure.

Very high levels of plasma renin activity were found in some of the hypertensive rats, whereas others had normal or below normal values. No correlation was found between plasma renin activity and blood pressure at this stage in the development of hypertension. This finding agrees with our previous observations[2] and suggests that other factors unrelated to hypertension are involved in the levels of renin secretion. In our studies of the renin-like activity present in the artery wall, a tendency to higher values in hypertensive animals was observed when compared with the normotensive or sham-operated rats. Nevertheless, because of the great scatter of the results, no statistically significant difference could be established. This behavior resembles that observed with plasma renin activity levels. Nevertheless, no correlation between plasma renin activity and renin-like activity present at the artery wall was found. Moreover, there was no correlation between the levels of renin-like activity present at the artery wall and blood pressure.

Table 5.—**Effect on Plasma Renin Activity of the Intravenous Injection of 0.2 GU of Purified Hog Renin**

		Plasma renin activity, mean ± SEM*				
			Minutes			
	No.	Before	5	15	30	60
Sham-operated rats	7	7.37 ± 1.95	37.26 ± 4.59	14.44 ± 1.38	9.23 ± 0.90	6.56 ± 1.07
Clip-operated rats	11	18.16 ± 9.12	76.08 ± 27.90	47.06 ± 17.85	29.14 ± 8.43	20.80 ± 4.16

*In nanograms of angiotensin I per milliliter per hour.
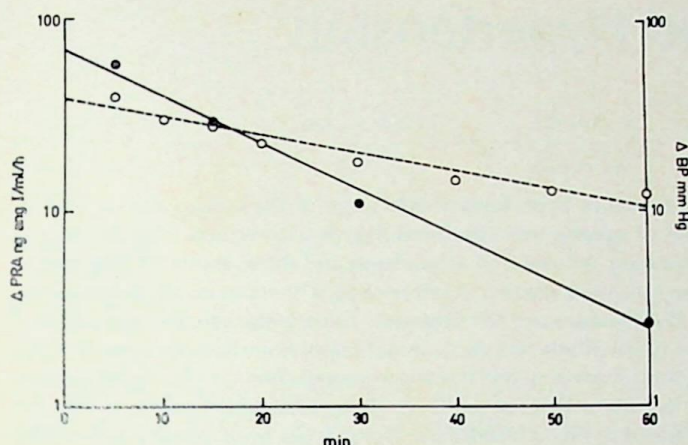
Fig. 2. Plasma renin activity and pressor response to renin at various time intervals after injecting purified hog renin into clip-operated rats. Other references as in Figure 1.

The potentiation of the pressor response to renin observed in one-kidney renal hypertensive and normotensive rats was similar but of less magnitude than that seen in bilaterally nephrectomized rats.[8] As is similarly observed after nephrectomy, this potentiation was partly caused by an increased half-life of circulating renin but mainly was the result of an enhanced binding of the enzyme to the artery wall. In sham-operated rats the renin response was also prolonged, although renin half-life did not differ statistically from that determined in normal animals.[8] Thus, a clear dissociation between the rate of disappearance of circulating renin and the pressor response to the enzyme was also observed in this group, although not associated with a significant increase in renin bound to the artery wall. A tendency to higher values of renin-like activity present at the artery wall after renin injection suggests that, in this group, 1 hour was possibly too long a period to demonstrate a differential binding of the enzyme to the artery wall.

Clipping one renal artery significantly potentiated the duration of the pressor response to renin, the half-life of renin, and the capacity of the artery wall to bind circulating renin. The protraction of the pressor response and the half-life of renin were the same whether hypertension developed or not; thus, the protracted response does not seem to be related to the presence of hypertension. What seemed to differentiate hypertensive from normotensive and sham-operated rats was the capacity of the arterial wall to bind circulating renin. When compared with sham-operated animals, both hypertensive and normotensive rats had a significantly higher level of renin bound to the blood vessels. The arteries from hypertensive rats bound even more renin than those from normotensive animals. Present results do not support the possibility that the capacity of the tissue to bind renin was related to the degree of hypertrophy or hyperplasia of the artery, because this increased capacity was present in normotensive rats that did not show a significant increment in the artery weight.

Some indirect evidence[6] raises the possibility that renin present in the artery wall may generate angiotensin locally, contributing to the maintenance of renal hypertension in rats with unilateral renal artery stenosis and contralateral nephrectomy. Present results were not able to confirm this hypothesis. Nevertheless, the difference found in the capacity of the arterial tissue to bind renin in this type of hypertensive rat indicates that the enzyme present in the blood vessels may play some role in the maintenance of hypertension.

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Altitude and Hypertension

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In order to study the prevalence of hypertension and some of the factors relevant to its natural history, cross-sectional surveys were performed during the period 1967 to 1973 in five small Peruvian communities, two located at sea level and three above 13,000 feet of altitude. In total, 4,359 persons were studied at sea level (1,970 males and 2,389 females) and 3,055 at high altitude (2,189 males and 866 females). At high altitude, the age-adjusted prevalence of hypertension (particularly systolic) was definitely low; diastolic hypertension was more frequent in men than in women, and it was commoner than systolic hypertension. The reverse was observed in communities at sea level. Long-term blood pressure changes observed in natives accustomed to high altitudes but living at sea level, as well as in white persons usually living at sea level but residing at high altitude, appear to indicate that environmental forces are more important than genetic predispositions in determining the rarity of hypertension in the highlands. Among the environmental forces, chronic hypoxia seems to play an important causal role.

During the last 2 decades, epidemiologic studies carried out in different parts of the world have yielded convincing evidence that average blood pressure values and the prevalence of hypertension rise with age. The increased blood pressure, with or without its deleterious consequences, constitutes the disease called primary or essential hypertension[1] in 90% or more of hypertensive individuals in most series. These facts have greatly stimulated research efforts aimed at a better understanding of the pathogenesis and management of the condition.

Many years ago, clinical observations suggested that arterial hypertension was a common disorder in populations living at sea level, whereas it was rare in the highlands. For this reason, in 1965 we started an epidemiologic investigation on cardiovascular diseases with the stimulus and support of the World Health Organization. The data that follow summarize our survey experience on the prevalence of hypertension in population groups inhabiting the central mountain areas of our country.

MATERIAL AND METHODS

During the period 1967 to 1973, blood pressure surveys were performed in five small communities of similar socioeconomic level. Two were located at sea level and three above 13,000 feet. This community approach permitted us to examine a total of 7,414 persons (4,159 males and 3,255 females). The response rate was high, ranging from 62.5 to 98.6%. The major characteristics of the population samples studied are shown in Table 1.

Systemic blood pressure was recorded by the auscultatory method (within incremental levels of 2 mm Hg) in the right arm with the subject in the sitting position. Special care was taken that subjects had not exercised, eaten, smoked, or been exposed to cold at least for the previous 30 minutes and that the sitting posture was maintained for no less than 5 minutes before pressure readings.[2] Blood pressure was recorded by the same three observers throughout.

To facilitate description of the findings, systolic pressures equal to or greater than 160 mm Hg and diastolic pressures equal to or greater than

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Table 1.—**Population Samples Studied**

Community	Year of study	Altitude, ft	Age of target population, yr	Sample size		
				Males	Females	Total
Puente Piedra	1972	Sea level	≥5	1,497	1,893	3,390
Infantas	1973	Sea level	≥5	473	496	969
Milpo	1967	13,450	≥15	816	216	1,032
Colquijirca	1968	13,975	≥15	625	95	720
Cercapuquio	1970	14,300	≥5	748	555	1,303

95 mm Hg were considered abnormally high, in accordance with the World Health Organization criteria for hypertension.[3] The prevalence of hypertension was calculated for each sex by decades of age, from 15 years of age and upward. Then, an overall figure was obtained by direct standardization[4] against the national population registered during the official census of 1972 to adjust for differences in age composition of the samples and to make the data more comparable. Differences between rates obtained at high altitude and at sea level, for males and females, and for systolic and diastolic hypertension were tested by the chi-square test.

RESULTS

The age-standardized prevalence, by sex, for systolic and diastolic hypertension obtained in each of the five communities studied is shown in Tables 2 and 3. The prevalence of systolic hypertension in males was at least 12 times higher at sea level than at high altitude ($P<0.001$). This difference was even higher in females with the exception of women of Colquijirca (Table 2, Fig. 1). In turn, diastolic pressure was also higher at sea level, but the differences were less striking than for systolic pressure, especially in males ($P<0.05$ to 0.001; Table 3, Fig. 2).

It is worth noting that, at sea level, hypertension tends to be more frequent in females and systolic hypertension is more common than diastolic; at high altitude the disorder is more frequent in men than in women and diastolic hypertension is more common than is systolic. All these facts emphasize the different natural history of hypertension at high altitude.

Table 2.—**Prevalence of Systolic Hypertension* at 15 Years of Age or Greater, by Sex†**

Community, altitude, year of study	Males		Females	
	%	SE	%	SE
Puente Piedra, sea level, 1972	70.0	9.9	100.7	9.3
Infantas, sea level, 1973	51.1	13.4	149.0	19.7
Milpo, 13,450 ft, 1967	3.1	2.0	3.3	3.9
Colquijirca, 13,975 ft, 1968	4.1	2.6	8.6	9.5
Cercapuquio, 14,300 ft, 1970	3.6	2.8	0.0	0.0

*Systolic blood pressure, ≥160 mm Hg.
†Age-adjusted rate × 1,000 population.

DISCUSSION

The study reported here has shown that arterial hypertension is rare in groups living in the high regions of our country. This is highly relevant, taking into account that age-specific prevalence of systolic and diastolic hypertension at sea level was found to be increased and similar, for instance, to that found in whites in the National Health Survey performed in the United States in 1960 to 1962.[5]

Table 3.—**Prevalence of Diastolic Hypertension* at 15 Years of Age or Greater, by Sex†**

Community, altitude, year of study	Males		Females	
	%	SE	%	SE
Puente Piedra, sea level, 1972	49.7	8.4	50.6	6.8
Infantas, sea level, 1973	35.0	11.2	85.4	15.5
Milpo, 13,450 ft, 1967	28.7	5.9	10.7	7.0
Colquijirca, 13,975 ft, 1968	15.5	4.9	8.6	9.5
Cercapuquio, 14,300 ft, 1970	9.6	4.6	6.1	4.6

*Diastolic blood pressure, ≥95 mm Hg.
†Age-adjusted rate × 1,000 population.

The low prevalence of hypertension at high altitude may be due to genetic predispositions or environmental forces, or both. The possible relative importance of both causal sources is briefly discussed below.

The Role of Heredity.—With the present geographic and socioeconomic characteristics of our country, populations living at the higher altitudes have a lesser degree of ethnic mixing than do those at low altitudes. The populations studied, however, are highly comparable in many respects and, though differences in ethnic composition persist, they do not suffice to explain the tremendous differences in the hypertension rates described. Three facts strongly suggest a minor influence of genetics on this subject.
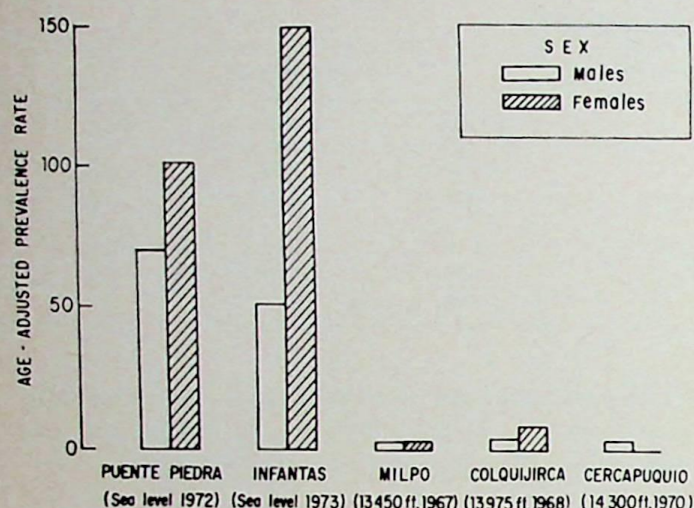
Fig. 1. Prevalence of systolic hypertension at sea level and at high altitude. Extremely high rates are seen at sea level, especially in women.

First, the blood pressure of natives living at high altitude increases on prolonged residence at sea level and tends to resemble the pressure values of natives of sea level.[6] Second, a retrospective observation of 100 white males originally from sea level, mostly from the United States of America and Europe, who lived for 2 to 15 years at an altitude of 12,398 feet, showed that they had lower blood pressure values at the end of their residence at high altitude than at the beginning.[7] This would not be the case if blood pressure values of highlanders were hereditary in origin. Third, preliminary observations have indicated that familial aggregation of blood pressure in people from high altitudes and from sea level is low and similar, leaving the major portion of the pressure variance to be explained by environmental factors.[8]

The Role of Environment.—Environment may influence the natural history of hypertension through the interaction of its sociocultural, biologic, chemical, and physical components. The sociocultural levels of the population samples examined were low in all cases, although slightly higher in those at sea level. Animals and plants existing in the Andes differ somewhat from those that are common at the coast, and this fact may suggest a favorable influence from the diet of natives, which is based mainly on carbohydrates and proteins of vegetable origin. In addition, the high mineral content of these areas may determine an increased intake of certain minerals, such as zinc. A number of studies have called attention, in recent years, to the possible influence of trace elements on human health and disease.[9] These aspects should be studied in detail.

Fig. 2. Prevalence of diastolic hypertension at sea level and at high altitude. Higher rates are seen at sea level, predominantly in women, whereas at high altitude there appears to be a male predominance.

Among the elements of physical environment, chronic hypoxia is the most important factor at high altitude. It is known that hypoxia determines functional and structural vascular changes, probably oriented to improve blood oxygen supply to the tissues. Vasodilatation and hypervascularization,[10,11] by diminishing peripheral resistance to flow, diminish systemic blood pressure. A lesser thickness of the aorta than at sea level,[12] and probably a greater elasticity of this vessel, and a slightly lower cardiac output[13] contribute to lower blood pressure too. This effect is counteracted by high-altitude polycythemia, which increases blood viscosity and peripheral resistance. From this interplay of factors result the lower pressure values and hypertension rates, which are more evident in females, who have lesser degrees of polycythemia and lower systolic pressures than males.[14] The finding of an enlarged carotid body in dwellers at high altitudes[15] opens the question of whether an impaired reflex blood pressure regulation also exists in these people.

In conclusion, the low prevalence of hypertension found in populations living at high altitude provides an epidemiologic basis for further investigation. The explanation of this finding is still far from clear but it seems to be evident that it is determined by the multifactorial influence of environment. The study of the renin-angiotensin system and of the kallikrein-kinin system in people born and living in an hypoxic environment and a prospective study of blood pressure in humans to assess if—within certain conditions—pressure values of those residing at sea level decrease with prolonged exposure to hypoxia constitute interesting areas for future study.

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50 Years Ago in *Proceedings*

"In recent years there has been a remarkable increase in the economic aspects of medicine which in the past has undoubtedly been neglected by the profession. The changing attitude of the public toward the medical profession, the changing methods in the practice of medicine itself, the development of social and state medicine in other countries, and the possibility of their being transplanted to our midst, have all presented problems which demand solution."

W. F. Braasch, M.D.
In a report to the staff of the
Minnesota State Medical Association.
Mayo Clinic Proceedings 2:149 (July 6) 1927

New Approaches to the Study of Angiotensin Tachyphylaxis

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Of the various mechanisms proposed to explain the development of tachyphylaxis, the initial step of drug-receptor interaction has received the most attention. The present study suggests that the affinity of angiotensin II itself or an angiotensin analogue for the angiotensin receptor is a determining factor in the development of tachyphylaxis. The concept of negative cooperativity is introduced as a consequence of the observed correlation in the present study between slopes of less than unity as determined in Hill plots and the development of tachyphylaxis.

The concept of receptors was first introduced by Ehrlich[1] in Germany and Langley[2] in England. They suggested that cell membranes include discrete areas with which certain biologically active compounds combine in order to induce a response, and they used the term "receptor" to describe such an area. One of the features of an agonist-receptor interaction appears to be, in many cases, the production of tachyphylaxis. Tachyphylaxis is an acute, specific desensitization in the sense that an agonist, on repeated application, will no longer induce its usual physiologic or pharmacologic response, but other agonists acting via different receptors still will be able to produce that response.

Tachyphylaxis to angiotensin II was first described by Page and Helmer,[3] in measuring the blood pressure response of the anesthetized dog. Repeated intravenous injection of angiotension II resulted in successively decreased pressor responses; pressor responses to norepinephrine were, however, unaffected. Various mechanisms have been proposed for the development of tachyphylaxis to angiotensin. It has been suggested that angiotensin II induces contractions of vascular smooth muscle by release of neuronal norepinephrine, and that tachyphylaxis develops as a result of depletion of these stores.[4] Although this has been reported to occur in mammalian aortas,[4,5] with reversal of tachyphylaxis to angiotensin II on incubation with norepinephrine, others have not been able to repeat these observations.[6]. It has also been suggested that an abnormal angiotensin II-receptor combination occurs, in which the histidine moiety in position 6 of the angiotensin II molecule combines with a hypothetic anionic site that is close to, but not part of, the angiotensin receptor.[7] This results in a "twisting" of the angiotensin II molecule. The recently reported findings of Paiva and associates[8] on the poor correlation between development of tachyphylaxis to angiotensin II and analogues on the rat uterus and the degree of protonation in position 6 of the angiotensin II molecule make this proposed mechanism unlikely. A good correlation has been reported between the ease of development of tachyphylaxis to angiotensin II and analogues on the rat uterus and the degree of protonation in position 1 of the angiotensin II molecule.[8] However, the analogue [Arg[1]] angiotensin II does not fit into this scheme.

We have recently reported[9] a high correlation between the affinity of an angiotensin analogue for its receptor and the induction of tachyphylaxis.

The aim of the present study was to further elucidate the role of affinity in the mechanism of development of tachyphylaxis to angiotensin II, by the use of Hill plots. A Hill plot is a mathematical expression of kinetic data of an enzyme reaction which, from the value of its slope, gives information as to the number of active sites involved in the reaction. Hill plots have also been constructed with data from dose-response curves,[10] in which case the slope determines cooperativity. Cooperativity describes an interaction between receptors such that occupation of a number of them either enhances (positive cooperativity) or inhibits (negative cooperativity) occupation of the remainder of them. A slope of less than unity in the Hill plot denotes negative cooperativity; greater than unity indicates positive cooperativity.

METHODS

Rabbit Aorta.—Female rabbits weighing between 1.5 and 3.0 kg were sacrificed by means of air emboli. The aorta was removed, cleaned, and stored in chilled physiologic salt solution. Spirally cut rabbit aortic strips, 4 to 6 cm long, were prepared according to the method of Furchgott and Bhadrakom.[11] They were mounted in a 10-ml organ bath containing Krebs' solution* at 37° C and aerated with 95% O_2:5% CO_2. The strips were placed under 2 g passive tension and allowed to equilibrate for 2 hours. Two cumulative dose-response curves were performed with each agonist, an interval of 30 minutes being allowed between dose-response curves. Values from the second dose-response curve were used for all calculations.

Rat Aorta.—Virgin female Sprague-Dawley rats (200 to 250 g) were killed by decapitation. The aorta was removed, cleaned, and stored in chilled physiologic salt solution. The procedure was then essentially the same as for rabbit aorta.

With each tissue, isometric contractions were recorded using a Grass force-displacement transducer (FT-03) on a Grass polygraph (Model 7). Values from the first cumulative dose-response curve were used for all calculations.

RESULTS

Hill plots of dose-response curves to angiotensin II and [Sar[1]] angiotensin II on the rabbit aorta and to angiotensin II on the rat aorta were constructed (Fig. 1). As responses to agonists are expressed in arbitrary units, the value of the slope of angiotensin II on the rabbit aorta is given the value *x*. The slope values for

*Krebs' solution (mM): NaCl, 117.9; $NaHCO_3$, 25.0; KCl, 4.69; $MgCl_2$, 0.54; NaH_2PO_4, 1.01; glucose, 11.1; $CaCl_2$, 2.52.
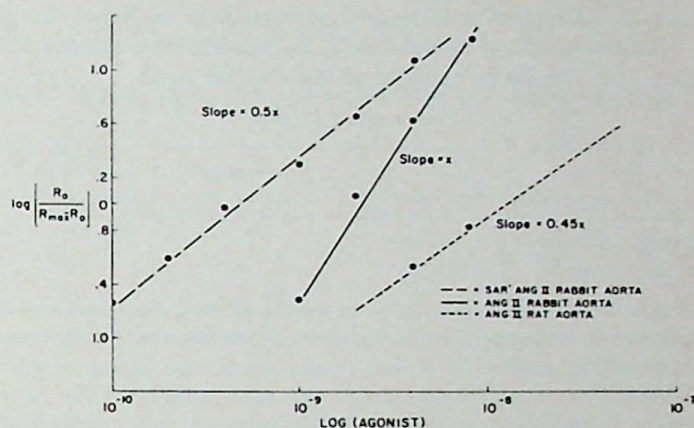
Fig. 1. Hill plot of responses to [Sar[1]] angiotensin II and angiotensin II on rabbit aorta and to angiotensin II on rat aorta. *R* is final response to that concentration of agonist at equilibrium, and is expressed in arbitrary units. Slope values are expressed relative to that of angiotensin II on rabbit aorta, which is termed x. Values are mean of four experimental determinations for each point.

[Sar[1]] angiotensin II on the rabbit aorta and angiotensin II on the rat aorta then become 0.5*x* and 0.45*x*, respectively.

If the slope of the angiotensin II dose-response curve on the rabbit aorta is taken as unity, an assumption validated by reported binding data of [^{3}H]angiotensin II to rabbit aorta,[12] then [Sar[1]] angiotensin II on the rabbit aorta and angiotensin II on the rat aorta exhibit slope values significantly less than unity, indicating negative cooperativity.

It has previously been shown that [Sar[1]] angiotensin II and angiotensin II act on the same receptor in the rabbit aorta[13] and that [Sar[1]] angiotensin II displays a greater affinity for this receptor.[13] Our results confirm this greater affinity in that, although [Sar[1]] angiotensin II displays negative cooperativity, experimental values are still displaced to the left of those for angiotensin II itself in the Hill plot.

As the maximum response to angiotensin II and [Sar[1]] angiotensin II is the same on the rabbit aorta, although occurring at different concentrations of agonist, it is unlikely that the observed negative cooperativity is simply a manifestation of a reduced contractile response. However, with the rat aorta this was a possibility because this tissue exhibits less responsiveness to angiotensin II than does the rabbit aorta.[14] Tachyphylaxis to [Sar[1]] angiotensin II was induced by performing a dose-response curve and then challenging the tissue 30 min later with either [Sar[1]] angiotensin II or angiotensin II itself; concentrations as high as 2×10^{-7} g/ml elicited no response (Table 1). However, on induction of tachyphylaxis to angiotensin II, a dose-response curve showed that

Table 1.—Effect of Induction of Tachyphylaxis to Either [Sar[1]] Angiotensin II or Angiotensin II on Subsequent Responses to These Peptides on Isolated Rat Aorta

Agonist used to induce tachyphylaxis	Subsequent response*		
	Angiotensin II	[Sar[1]] angiotensin II	Concentration, g/ml
[Sar[1]]angiotensin II	0	0	2×10^{-7}
Angiotensin II	0	17 ± 9	10^{-8}
	0	43 ± 5	2×10^{-7}

*Response expressed as percentage of maximum response to angiotensin II (n = 4).

although again no response was obtained to concentrations of angiotensin II up to 2×10^{-7} g/ml, concentrations of [Sar[1]] angiotensin II as low as 10^{-8} g/ml induced a significant response (Table 1).

DISCUSSION

The most commonly accepted mechanism of development of tachyphylaxis to angiotensin II is that proposed by Page and Bumpus.[15] Occupation of its receptor by the angiotensin II molecule prevents further occupation and stimulation, and hence induces specific desensitization.

The development of tachyphylaxis to isoproterenol by β-adrenergic receptors in the rat pineal gland[16] and the frog erythrocyte membrane[17] does not appear to involve negative cooperativity. A decrease in the available number of receptors does occur, but these remaining receptors show no decrease in affinity.

We propose the following scheme for the development of tachyphylaxis to angiotensin II by the rat aorta: occupation of receptors by angiotensin II limits the number of remaining available receptors for stimulation and also greatly reduces the affinity of these remaining receptors for angiotensin II. The reduction in number and affinity is suggested by the observation that after induction of tachyphylaxis to angiotensin II on the rat aorta, attempted "flooding" of remaining receptors with large concentrations of angiotensin II induces no response, but the higher affinity analogue, [Sar[1]] angiotensin II, does induce a significant response.

We realize that the site of negative cooperative interaction may not be the angiotensin II-receptor complex but a point beyond this in the transduction of the response. We are now undertaking studies involving binding [^{3}H]angiotensin II to smooth muscle cell membranes in order to examine the role of the angiotensin II-receptor complex in this process.

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Role of Naturally Occurring Vasoactive Principles in Hypertension

STATE OF THE ART

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Hypertension may result from excessive activity of one or more components of the blood pressure-elevating system. These include the adrenergic nervous system, the renin-angiotensin axis, and mineralocorticoids (aldosterone), which potentiate each other, reinforcing their effects on renal hemodynamics and electrolyte transport and thereby affecting extracellular fluid volume, vascular tone, and reactivity. We consider of no less importance in the genesis of hypertension the failure of one or more components of the blood pressure-lowering system: the kallikrein-kinin system, prostaglandin, or one or more lipids associated with the renomedullary interstitial cells. As a corollary of this hypothesis, if one assumes tonic activity of these opposing blood pressure-regulating systems, in the case of a deficiency of the vasodepressor system, hypertension should result. That is, unopposed activity of the pressor system should be sufficient to increase blood pressure without an increase in the "basal level" of its activity. Hypertension, then, may be considered to result from either uncompensated deficiencies or excesses, which may be relative or absolute, of one or more components of the vasodepressor and vasopressor systems.

Classic studies performed more than 30 years ago demonstrated that the clamping of one renal artery in the dog induced a transient hypertension for about 3 weeks, followed by a return of blood pressure to the normal level.[1] Removal of the contralateral kidney in these animals reelevated blood pressure and this increase was sustained. However, if a renal transplant from a normal dog was performed in a previously hypertensive animal, blood pressure returned to normal levels (Fig. 1).

These important observations suggested a dual blood pressure regulatory function of the kidney and led Fasciolo to propose the "protective action of the normal kidney."[2] In the following years, the prohypertensive as well as antihypertensive function of the kidney was evaluated by Grollman and associates,[3] who anticipated the relative significance of pressor and antipressor factors. Recent studies on antihypertensive mechanisms, which have included the local generation and release of antihypertensive substances from various organs and tissues (for example, kidney, uterus, and blood vessels), have resulted in renewed impetus to the characterization of those compounds that lower blood pressure. These studies suggest that hypertension results from an imbalance of agents that have opposing actions on blood pressure. We will discuss here the antihypertensive mechanisms that operate through the release or formation of vasodepressor or antihypertensive substances in various organs—substances that have the capacity to attenuate or modulate the effects of the vasoconstrictor hormones.

ANTIHYPERTENSIVE FUNCTION OF THE KIDNEY

The possible beneficial effect of a renal principle for the treatment of hypertension was demonstrated more than 40 years ago when Dadlez and Koskowski[4,5] described the diuretic and antihypertensive effect of renal extracts in men and rabbits and when Gomez[6] showed an antihypertensive

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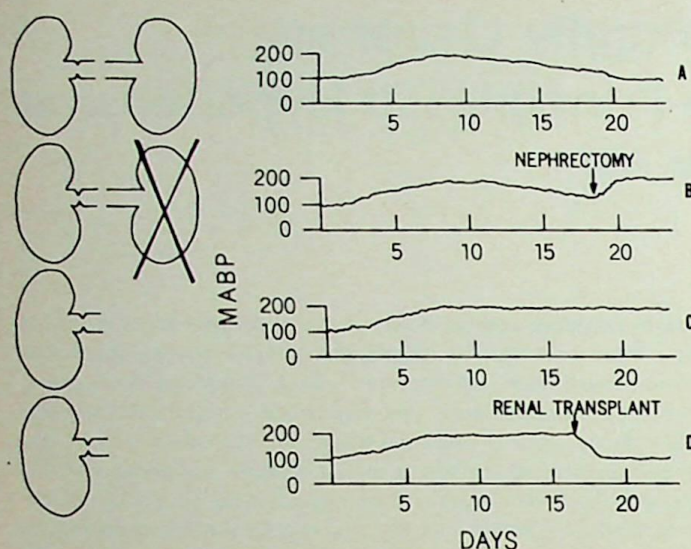
Fig. 1. Effect of unilateral renal ischemia on mean aortic blood pressure (*MABP*) of dogs. *A*, Under these conditions if contralateral kidney is left intact, increase in MABP is usually transitory. *B*, If normal kidney is removed when blood pressure is decreasing, MABP rapidly increases and sustained hypertension develops. *C*, Sustained elevation of MABP also results from inducing renal ischemia in uninephrectomized animal. *D*, If transplant of normal kidney is performed during hypertensive state, MABP falls to normal levels.

effect of these extracts in hypertensive but not in normal patients. In 1940, Grollman and associates[7,8] confirmed these observations and showed that renal extracts reduced the blood pressure of hypertensive rats and man. The aqueous extract obtained after several forms of isolation was found to be relatively insoluble in organic solvents and was considered to be a peptide[9] of cortical origin.[10] In the early forties, Page and associates[11-14] described a prolonged decrease in blood pressure induced by a nondialyzable substance extracted from kidney, muscle, and lung. The intramuscular or subcutaneous administration of this extract decreased blood pressure in rats, dogs, and patients who had essential and malignant hypertension. The patients with malignant hypertension had a striking improvement in ocular changes and renal function, but frequent toxic reactions (shock, fever, and local inflammation) precluded the use of the extract on a wider scale.[14] Several years later, Milliez and associates[15-17] demonstrated, in acetone extracts of hog and rabbit kidney, a vasodepressor principle characterized as a lipid which lowered blood pressure in hypertensive rabbits. The above studies suggested that the kidney is a source of antihypertensive substances and provided the basis for those that are to be considered in this review.

Renin Inhibitor.—Activation of acylhydrolases results in the liberation of several vasoactive substances such as lysophospholipid[18] and arachidonic acid; the latter is the unsaturated fatty acid precursor of renal prostaglandins. Sen and associates[19] isolated from dog's kidney a phospholipid that can inhibit the in vitro generation of angiotensin by dog renin from renin substrate and the in vivo responses to injected renin. This compound is also able to decrease blood pressure in renal hypertensive rats but not in normotensive rats[19-21] (Fig. 2). A high amount of arachidonic acid is present in this phospholipid, which has been proposed to exist in two forms: as an inactive phospholipid precursor, "renin preinhibitor," and in an active form, the lysophospholipid "renin inhibitor" enzymatically formed by phospholipase A.[20,21] This renin inhibitor system, therefore, depends on the level of activity of phospholipase A, an enzyme directly related to the release of fatty acid precursors of prostaglandins. It appears that phospholipase A may be the controlling factor in the production of prostaglandins and the lysophospholipid "renin inhibitor" in tissues. However, the intrarenal function of the latter is still uncertain.

Antihypertensive Principle of the Renal Medulla.—Based on strong evidence that the normal kidney exerts a nonexcretory antihypertensive function, Muirhead and associates[22] performed studies in order to identify the renal structure responsible for that beneficial effect. In 1960, they reported that auto-
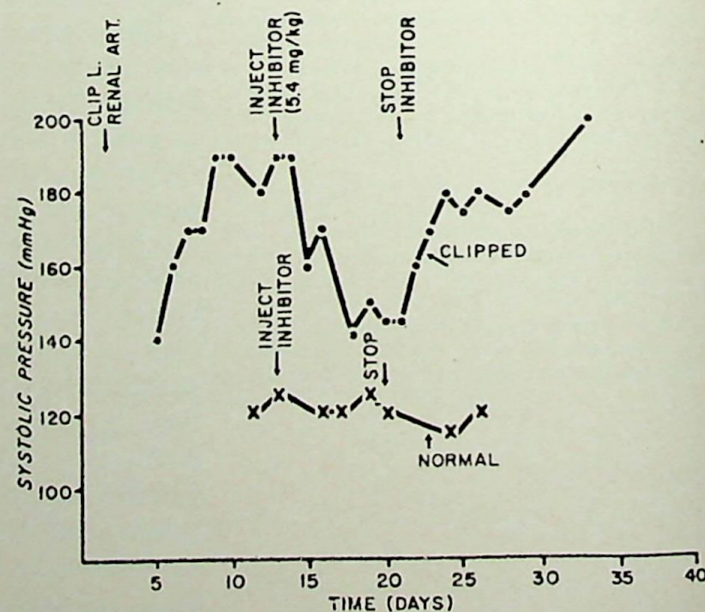
Fig. 2. Responses of clipped renal hypertensive rat (· —— ·) and normal rat (x-x-x) to daily intramuscular injection of phospholipid renin inhibitor. Compound decreased blood pressure in hypertensive rats and produced no changes when administered to normotensive rats in same dose range. (From Smeby RR, Sen S, Bumpus FM: A naturally occurring renin inhibitor. Circ Res 20-21 Suppl 2:129-134, 1967. By permission of the American Heart Association.)
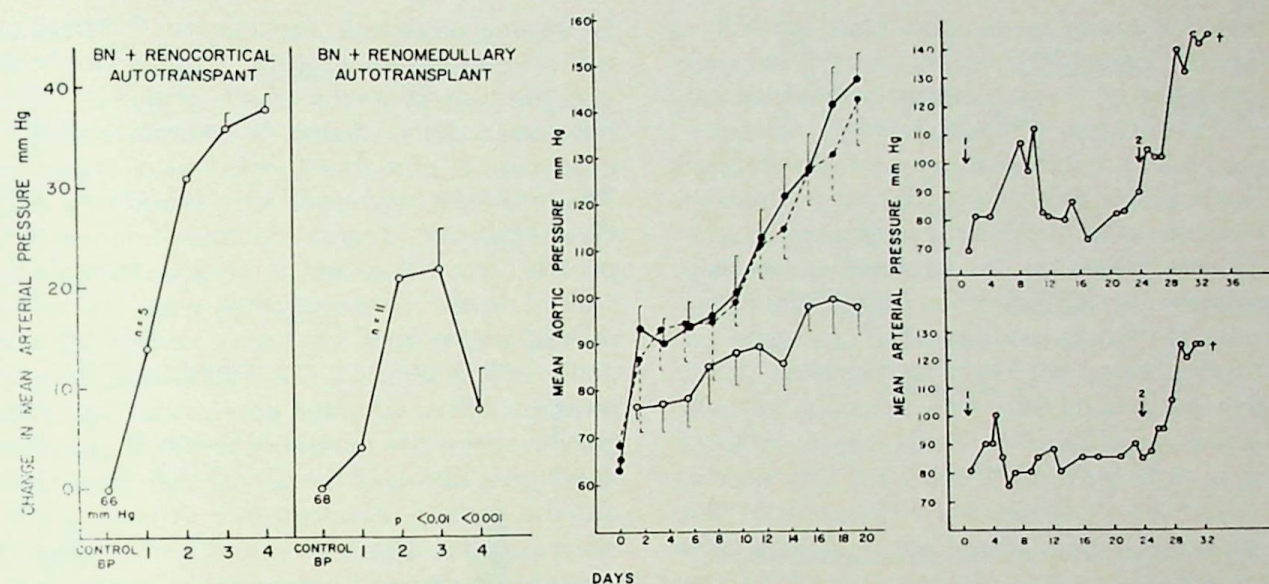
Fig. 3. Two panels on left demonstrate effect of autotransplants of renal cortex and renal medulla on renoprival hypertension of rabbit due to extreme sodium loading (~9 meq/kg per day). Renocortical autotransplants failed to protect against this hypertensive state. Renomedullary autotransplants caused lag in pressure elevation for 2 days, followed by return of pressure to near baseline levels by fourth day. *BN* = bilateral nephrectomy. Middle panel demonstrates protection against malignant hypertension of rabbit by renomedullary autotransplants (open circles, solid line) and failure of such protection by renocortical autotransplants (solid circles, broken line). Blood pressure of control group is displayed by solid circles with solid line. Panel on right shows what happened when renomedullary transplants protective against malignant hypertension were removed (*arrow 2*). Arterial pressure increased sharply and animals died. (Modified from Muirhead and associates.[38,39])

transplants of renal medulla prevented renoprival hypertension in the dog. This effect was not observed in animals in which transplants of renal cortex, spleen, or liver were used and led the authors to propose that renal medullary tissue is responsible for the antipressor action of the kidney. This preliminary observation provided the basis for many other studies which resulted in the extraction, from the renal medulla, of various vasoactive lipids with antihypertensive properties. Some of them were characterized as prostaglandins and others as neutral lipids.[23-33]

The presence of these vasoactive compounds in the renal medulla led Muehrcke and associates[34,35] to investigate the possible participation of the renal medullary interstitial cells in the formation of antihypertensive substances. They demonstrated a significant reduction of the lipid granules in the medullary interstitial cells of the kidney from DOCA-salt hypertensive rats and men with malignant hypertension, observations that were confirmed by Tobian and his group in Goldblatt and sodium-loaded hypertensive rats.[36,37] Further support for the antihypertensive action of the renal medulla was provided by Muirhead and associates,[38,39] who showed that autotransplants of renal medullary tissue prevented the development of malignant hypertension in one-kidney Goldblatt hypertensive rats and rabbits and in sodium-loaded renoprival hypertensive rabbits. This beneficial effect was not obtained with autotransplants of the renal cortex. Furthermore, if after a period of protection the transplants were removed from the Goldblatt rabbits, the blood pressure sharply increased and these animals died within 3 to 21 days[38,39] (Fig. 3).

As a consequence of these studies, interest was focused on the renal medullary interstitial cells; these elements were isolated from the rabbit renal medulla and grown in tissue culture as a monolayer. Using transplants of these cell cultures derived from the renal medulla, Muirhead[40] succeeded in reproducing the same effects in malignant hypertensive animals as those obtained by renal medullary transplants. Later, lipid extracts obtained from lapine renomedullary interstitial cell cultures were shown to possess a similar antihypertensive action in the sodium-volume dependent hypertensive rats.[41] This strongly suggested that the renal medullary interstitial cells situated between the vasa recta, the loop of Henle, and the collecting duct[42] might be important elements in the nonexcretory antihypertensive function of the kidney.

Renal Prostaglandins.—The range of products arising from the prostaglandin synthetase complex includes the primary prostaglandins of the D, E, and F series, the endoperoxides, and the thromboxanes, as well as other biologically active cyclicized deriva-
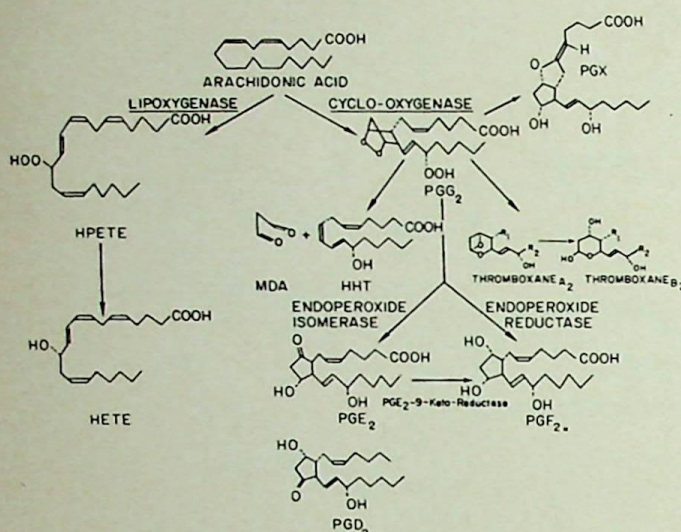
Fig. 4. Overall pathway in biosynthesis of prostaglandins from arachidonic acid.

tives[43-47] (Fig. 4). The principal prostaglandins, PGE_2 and $PGF_{2\alpha}$, have been identified in several organs, including the kidney.[28-31,33] Most, if not all, prostaglandins of the E and F series are removed or inactivated on passage across the lungs after release into the circulation from their organ of synthesis,[48] thereby suggesting that they belong to that group of hormones having circumscribed activity—the local or tissue hormones.

In addition to potent vasodilator (PGA and PGE)[49,50] and venoconstrictor (PGF)[51,52] actions, prostaglandins may function as modulators of the adrenergic nervous and renin-angiotensin systems. Thus, prostaglandins of the E series usually attenuate adrenergic activity,[53] while those of the F series may have an opposite effect, facilitating adrenergic transmission.[54] These properties of prostaglandins of the E series which antagonize the vasoconstrictor effects of pressor stimuli[55-57] have been demonstrated in chloralose-anesthetized dogs during intra-arterial infusion of angiotensin II. This resulted in decreased renal blood flow and urine flow; however, despite continued infusion of the peptide, blood flow and urine flow returned toward control levels concomitantly with the release of prostaglandins from this organ. When the administration of angiotensin II was not followed by release of prostaglandins, or after administration of prostaglandin synthetase inhibitors, the vasoconstrictor and antidiuretic effects of the polypeptide persist throughout the period of infusion.[55] Aiken and Vane[58] confirmed this observation and further showed that when prostaglandin release was prevented by a prostaglandin synthetase inhibitor, indomethacin,[59] the vasoconstrictor effect of angiotensin II in the kidney was substantially potentiated (Fig. 5). Moreover, activation of the renin-angiotensin system by inducing unilateral renal ischemia produced an increase in prostaglandin concentration in renal venous blood of the ischemic as well as the contralateral kidney. Infusion of exogenous PGE_2 into the renal artery also opposed the vasoconstrictor and antidiuretic effects of pressor stimuli.[57]

The importance of the prostaglandin biosynthetic capacity of the kidney has been shown in the acutely stressed dog. Under these conditions, the renal circulation is maintained by a major prostaglandin component, abolition of which by inhibition of prostaglandin synthesis results in a precipitous decline in renal blood flow.[60] However, in the conscious dog,
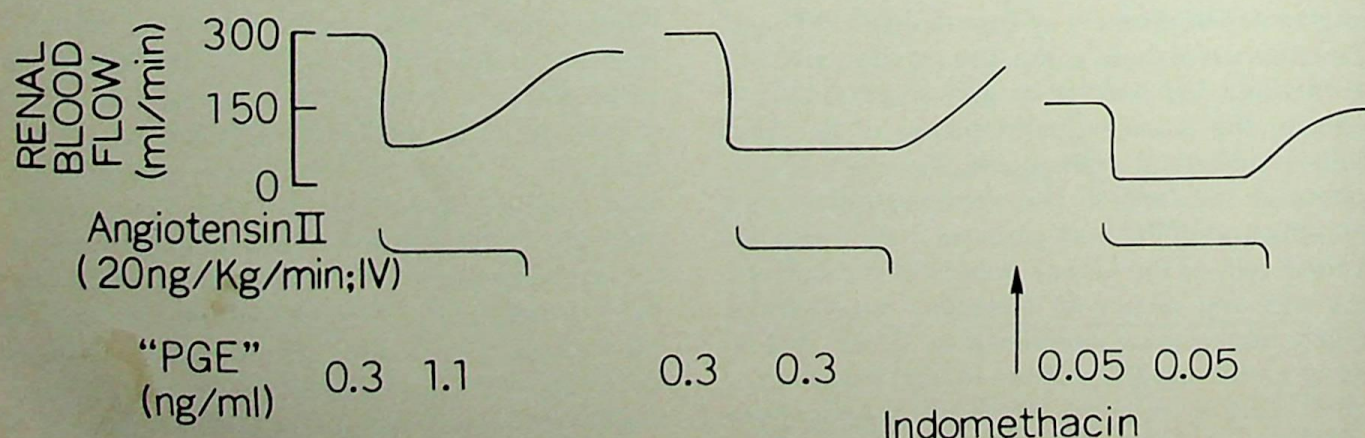
Fig. 5. Representation of renal vasoconstrictor action of angiotensin II, infused for 10 minutes in anesthetized dog, and related changes in renal venous prostaglandin concentrations. Left to right: despite continuous infusion of angiotensin II, pressor effect of drug is attenuated with fourfold increase of PGE_2. Vasoconstrictor effect of angiotensin II persists during complete period of infusion when no changes occur in PGE_2 concentration in renal venous blood. After prostaglandin synthesis inhibition by indomethacin, vasoconstrictor effect of angiotensin II is maintained during complete period of infusion. (From McGiff JC, Vane JR: Prostaglandins and the regulation of blood pressure. Kidney Int 8 Suppl 5:262-270, 1975. With permission.)
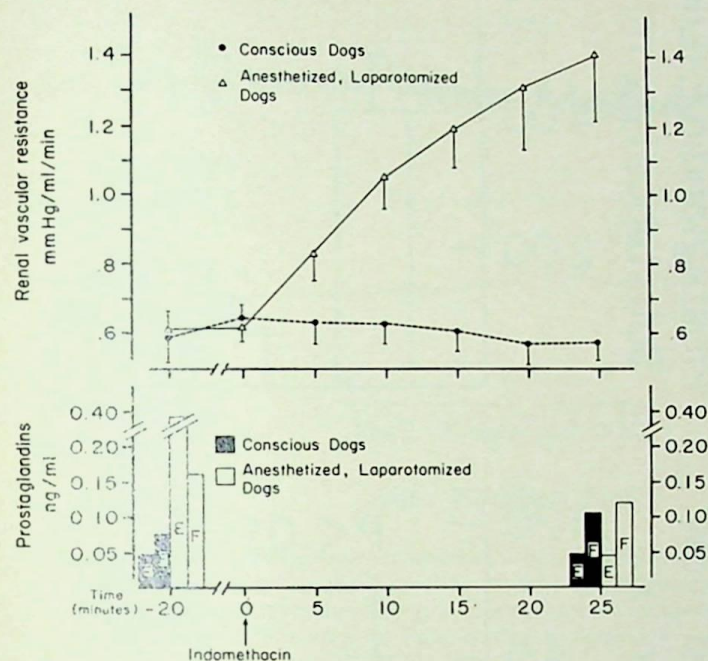
Fig. 6. Differential effect of indomethacin in surgically stressed dogs and in conscious dogs. High levels of prostaglandins antagonize vasoconstrictor effect of activated renin-angiotensin system in anesthetized, laparotomized dogs. Under these conditions, inhibition of prostaglandin system results in predominantly vasoconstrictor effect. In conscious animals, prostaglandin levels are very low and indomethacin fails to inhibit this basal synthesis. (From Terragno NA, Terragno DA, McGiff JC: Contribution of prostaglandins to the renal circulation in conscious, anesthetized and laparotomized dogs. Circ Res [in press]. By permission of the American Heart Association.)

indomethacin in intravenous doses as high as 10 mg/kg intravenously did not affect renal blood flow, mean aortic blood pressure, or renal venous prostaglandin levels, whereas in dogs under acute stress (anesthesia and laparotomy), administration of indomethacin (intravenously, 2 mg/kg) decreased renal blood flow by more than 40% despite an increased mean aortic blood pressure of 15%. These changes were associated with a decline in concentrations of renal venous prostaglandins to those levels observed in conscious animals[61] (Fig. 6). Furthermore, in the conscious dog, the principal renal prostaglandin appeared to be PGF because these values were twofold to threefold greater than those of PGE, whereas in acutely stressed dogs, the renal venous concentrations of PGE were more than twofold those of PGF. In both experimental conditions, plasma renin activity was highly correlated with PGE, but not with PGF, levels in renal venous blood. This study strongly suggests that (1) the effects of prostaglandin synthetase inhibitors on the renal circulation depend on the degree of activation of the renin-angiotensin and prostaglandin systems,[60,62] and (2) increased plasma renin activity and attendant augmented renal vascular resistance are modified by a protective mechanism that operates through prostaglandin release (Fig. 6).

Romero and co-workers[63,64] were the first to demonstrate the capacity of indomethacin to decrease plasma renin activity in normal and renal hypertensive rabbits. More recent observations clearly demonstrate a relationship between the renin-angiotensin system and prostaglandins at the level of renin release. Thus, the interaction between these systems is not unidirectional; prostaglandins and their precursors can also affect the release of renin in addition to the well-known capacity of angiotensin II to release prostaglandins. Larsson and associates[65] showed that arachidonic acid increased and indomethacin decreased plasma renin activity in the rabbit. Later, the same investigators[66] demonstrated that, on incubation of slices of renal cortex, renin release increased with the addition of arachidonic acid and endoperoxides (PGG_2, and PGH_2) to the incubation medium; however, the principal renal prostaglandins, PGE_2 and $PGF_{2\alpha}$, did
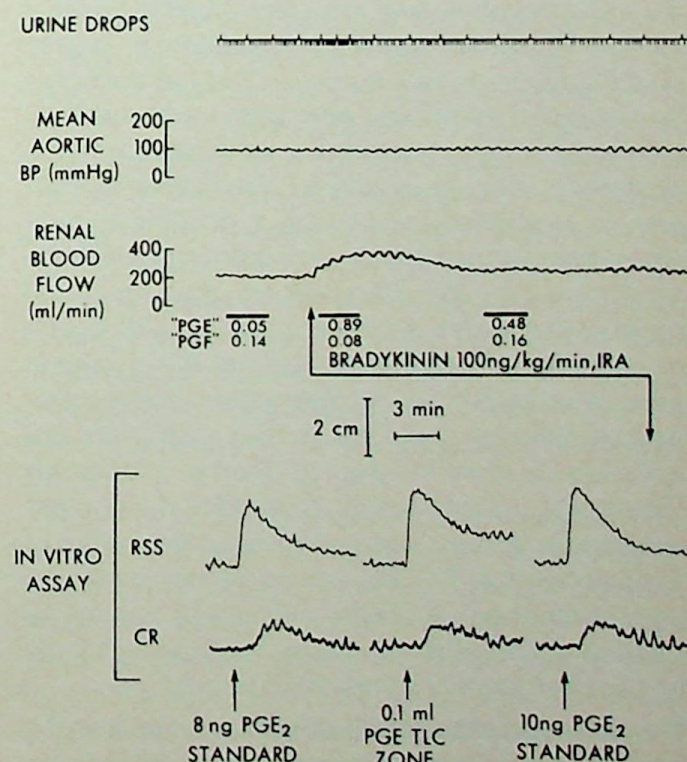
Fig. 7. *Upper*, Effect of infused bradykinin into renal artery (*IRA*) in chloralose-anesthetized dog. Times of renal blood collections are indicated by black bars. Concentration of prostaglandin E-like and F-like substance (*"PGE," "PGF"*) in renal venous blood is expressed as PGE_2 equivalents in nanograms per milliliter of blood. *Lower*, Bracket bioassay, used in determination of PGE after thin-layer chromatography. *RSS* = rat stomach strip; *CR* = chick rectum. (From McGiff JC, Terragno NA, Malik KU, et al: Release of a prostaglandin E-like substance from canine kidney by bradykinin: comparison with eledoisin. Circ Res 31:36-43, 1972. By permission of the American Heart Association.)

not stimulate renin release. An interaction between pressor and depressor systems was also demonstrated in studies performed on patients with Bartter syndrome. In this disease it was found that, in addition to hyperreninemia, hyperaldosteronism, and normal blood pressure, which characterize the syndrome,[67,68] urinary levels of PGE_2 were greatly increased. Treatment with indomethacin resulted in decreased plasma renin activity and, consequently, reduction of the accompanying secondary hyperaldosteronism as well as reduction of its expected effects on lowering prostaglandin levels. Because of the effects of indomethacin and arachidonic acid on release of renin, an intermediary product of prostaglandin synthesis, perhaps a prostaglandin endoperoxide, may be responsible for regulating renin release.

Renal Kallikrein-Kinin System.—Evidence that the kallikrein-kinin system might be involved in the hypertensive state was provided by Croxatto and San Martin[69] when they showed that urinary kallikrein, an enzyme that converts the precursor, kininogen, to kinin, was decreased in some forms of experimental hypertension. These observations were confirmed by studies of Margolius and associates,[70] who found a reduction in urinary kallikrein excretion in hypertensive but not in normal humans. This did not occur in hypertension associated with primary hyperaldosteronism, in which state urinary kallikrein excretion is increased. Altered activity of the kallikrein-kinin system in hypertension suggests a possible participation of this system in the development of some forms of hypertension. We have shown that intrarenal infusion of bradykinin increased renal blood flow and urine excretion, effects that are associated with release of prostaglandin.[71,72] These observations suggest that prostaglandins may contribute to the vasodilatory and diuretic effects of kinins (Fig. 7). Further support for the intrarenal interactions of the kallikrein-kinin and prostaglandin systems was provided by the studies of other investigators.[73-75] They demonstrated increased release of renal prostaglandin induced by enhancing the activity of the kallikrein-kinin system through long-term administration of mineralocorticoids.

The demonstration that bradykinin stimulated the release of prostaglandin does not necessarily indicate a direct effect on prostaglandin synthesis. Thus, mepacrine, a phospholipase A inhibitor, was suggested to prevent the release of prostaglandin from the guinea pig lung that is evoked by bradykinin, but not the release of prostaglandin produced by arachidonic acid. Therefore, it would appear that kinins stimulate prostaglandin release by activating phospholipase, which makes more substrate available to prostaglandin synthetase.[76]
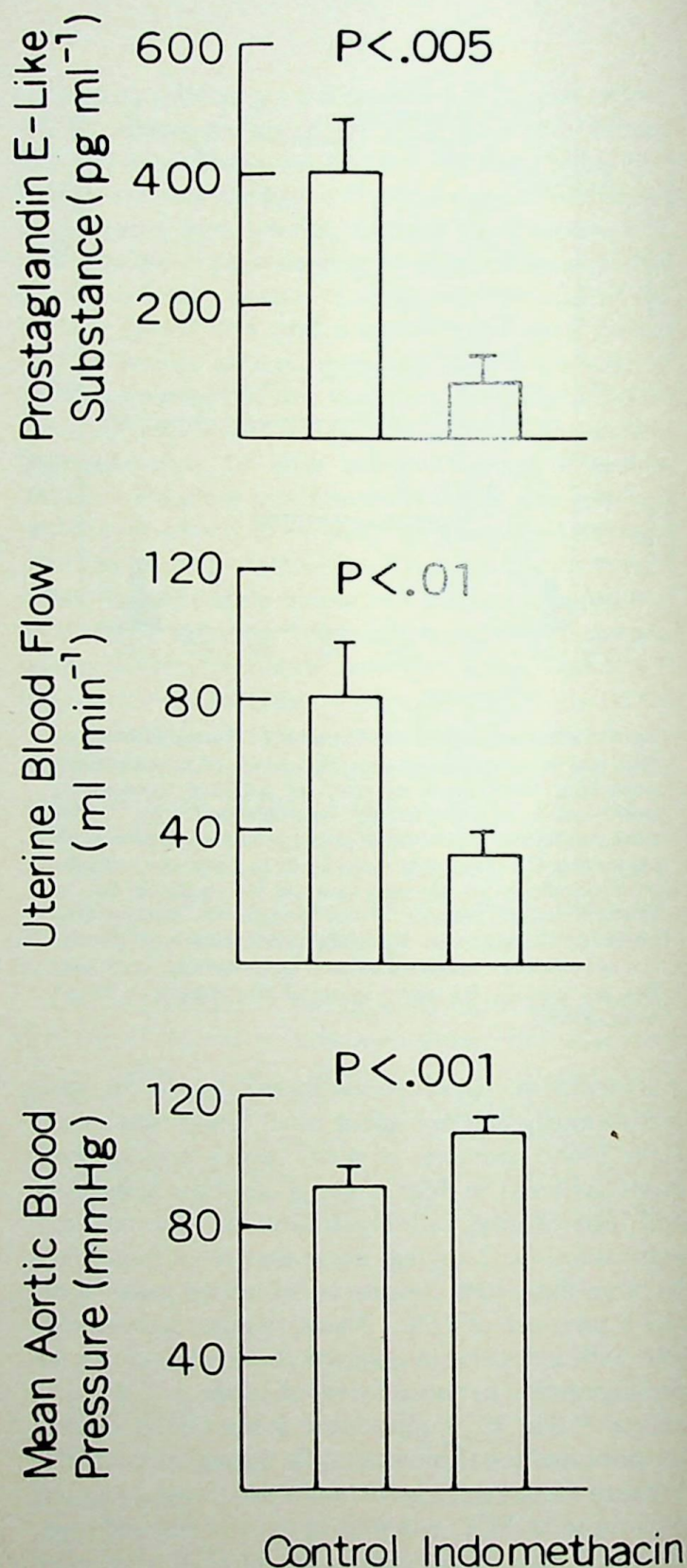
Fig. 8. Effects of intravenous injection of indomethacin (10 to 25 mg/kg) on concentration of prostaglandin E-like substance in uterine venous blood, uterine blood flow (of one horn), and mean aortic blood pressure in dogs during late pregnancy. Columns represent mean values and vertical bars represent standard error of mean. (From Terragno NA, Terragno A, McGiff JC: Prostaglandin E-angiotensin II interactions in the gravid uterus. Acta Physiol Lat Am 24:550-554, 1974. By permission of Asociación Latinoamericana de Ciencias Fisiologicas.)
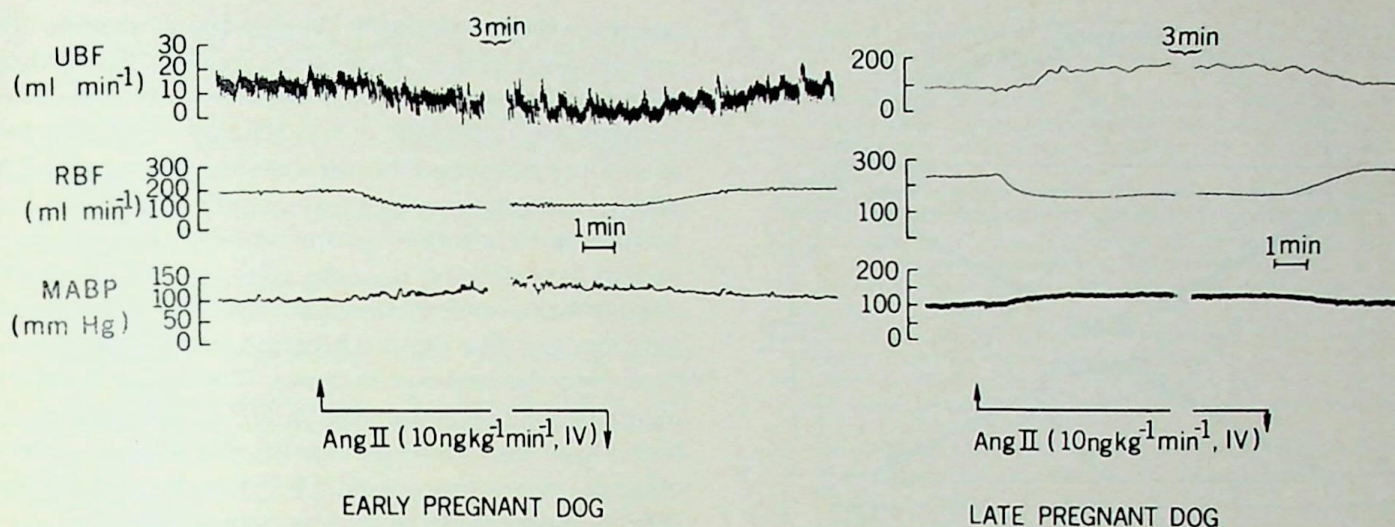
Fig. 9. Effect of intravenous administration of angiotensin II (*Ang II*) in early (*left*) and late (*right*) pregnancy on uterine blood flow (*UBF*), renal blood flow (*RBF*), and mean aortic blood pressure (*MABP*) in chloralose-anesthetized dogs. (From McGiff JC, Malik KU, Terragno NA: Prostaglandins as determinants of vascular reactivity. Fed Proc 35:2382-2387, 1976. By permission of Federation of American Societies for Experimental Biology.)

Another possible interaction of kinins and prostaglandins derives from the capacity of bradykinin to stimulate PGE 9-ketoreductase,[77] an enzyme that activates the conversion of PGE to PGF.[78] The physiologic significance of this effect of kinins, however, remains to be established. The previous observations that suggested that prostaglandin contributes to the effects of kinins should be considered when the possible participation of the kallikrein-kinin system in antihypertensive events is studied.

The Antihypertensive Function of the Pregnant Uterus.—Several investigators have demonstrated that pregnancy has a beneficial effect on increased blood pressure. Harrison and associates[79] and Grollman,[80] in the 1940's, observed that blood pressure decreases to near normal levels in hypertensive rats at the end of pregnancy and proposed that the fetal kidneys could be responsible for this antihypertensive effect. In addition, Page and associates[81,82] demonstrated the capacity of deciduomas to reduce blood pressure in hypertensive rats. Recently, Aoi and associates[83] confirmed the decrease in blood pressure to normal levels in spontaneously hypertensive rats a few days before delivery.

A first step in the assignment of a role to prostaglandins in regulating blood pressure during pregnancy rests on the demonstration that withdrawal of their influence will effect an increase in blood pressure and other hemodynamic changes associated with toxemia. We have reproduced some of these changes acutely in anesthetized pregnant dogs after inhibiting prostaglandin synthesis (Fig. 8). We have also shown that in late pregnancy (when the concentration of prostaglandins in uterine venous blood was high) the intravenous infusion of angiotensin II (10 to 37.5 ng/kg per minute), which increased the blood pressure by 20 mm Hg, also increased uterine blood flow and released a PGE-like material into the uterine venous blood.[84-86] This reversal of the effect of angiotensin II on uterine blood flow appeared to be related to the capacity of the uterus in late pregnancy to synthesize prostaglandins, because infusion of angiotensin II in early pregnancy or in nonpregnant animals (when prostaglandin concentrations in uterine venous blood are low) decreased uterine blood flow and increased blood pressure. Further, when prostaglandin synthesis is blocked by indomethacin, the uterine vasodilator effect of angiotensin in late pregnancy is abolished (Fig. 9).

Not only was there a release of prostaglandins from the gravid uterus in response to vasoconstrictor hormones but partial constriction of the canine uterine artery in late pregnancy also resulted in increased release of prostaglandins into uterine venous blood. The latter state was associated with progressive vasodilation in the ischemic uterus, suggesting that in response to acute ischemia, the uterus increased the release of a vasodilator material (PGE_2) to compensate for the decreased flow. Chronic uterine ischemia in baboons has been shown by Cavanagh and associates[87] to result in a state indistinguishable from toxemia of pregnancy—namely, hypertension and proteinuria. In addition, using light microscopy, electron microscopy, and immunofluorescence studies, the renal lesions are noted to be indistinguishable from those found in women with toxemia.[87] We have
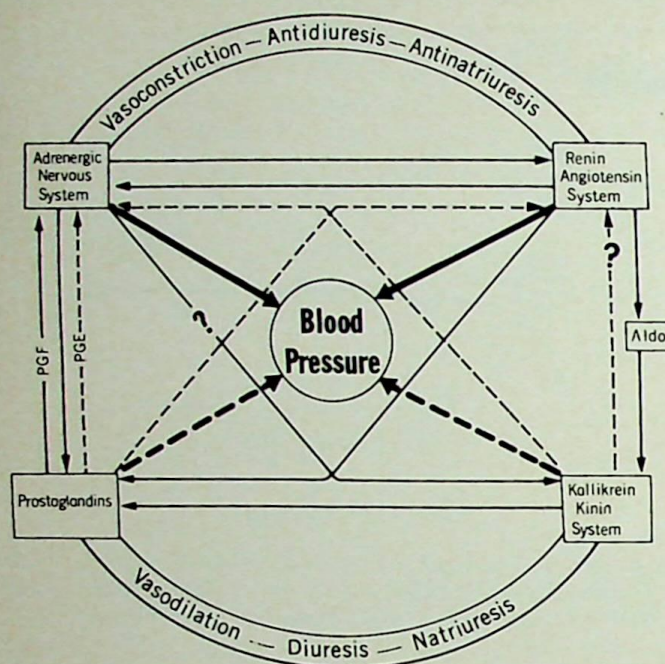
Fig. 10. Prohypertensive and antihypertensive mechanisms as affected by neurohormonal interactions. Possible interrelationships of blood pressure lowering and elevating hormones. Prostaglandins possess dual effects: PGF compounds and PGE compounds potentiate and attenuate, respectively, adrenergic nervous activity. Some of these relationships are very tentative, having been developed from preliminary observations—for example, attenuation by kinins of adrenergic nervous activity. Other interactions are seemingly paradoxical—that is, activation of renal kallikrein by renin-angiotensin system. Suggested dependency of latter on mineralocorticoid production is indicated by interposed box containing *Aldo*. *Solid line* = activation; *broken line* = attenuation; *Aldo* = aldosterone.

measured prostaglandin levels in the caval blood of these animals (that is, proximal to the major site of their degradation in the lungs) and have found them to be less than those of normotensive control values in the same animal.

A prostaglandin of the E series within the uteroplacental circulation could subserve this modulatory antipressor function.[84-86,88,89] Nevertheless, in view of the recent demonstration that umbilical blood vessels synthesize thromboxane,[90-92] as well as the recent report that a metabolite, 6-oxo-$PGF_{1\alpha}$ of a newly identified prostaglandin, PGX, or prostacyclin, is found in the uterus,[93] it would be premature to assign one product of prostaglandin synthetase a dominant role in the regulation of uterine vascular resistance or systemic blood pressure (Fig. 4). Functional interaction between the prostaglandin and kallikrein-kinin systems is not restricted to the kidney. In dogs in late pregnancy, we have demonstrated that intra-arterial infusion of bradykinin increased uterine blood flow coincident with a large release of prostaglandins into uterine venous blood.[84] When these studies are considered together, it becomes evident that prostaglandin interactions with pressor and depressor systems are important in the regulation of systemic blood pressure and blood flow to the uterus. In addition, production of prostaglandins by the gravid uterus may contribute to the amelioration of antecedent hypertension in some subjects and of experimental forms of hypertension. On the other hand, deficiency of this uterine function in pregnancy may determine the onset of toxemia. The capacity of the uterus to synthesize prostaglandins in late pregnancy seems to protect this organ against the vasoconstrictor effect of pressor hormones;[84-86,88,89] in this respect, the uterine vasculature resembles that of the kidney.[55]

Vascular Synthesis of Prostaglandins.—The possibility that prostaglandins of renal or other origin effect the general circulation is unlikely because prostaglandins are largely inactivated by the lungs.[48] The presence of norepinephrine, renin,[94,95] and prostaglandin-synthesizing enzymes in vascular tissues[50,96] and the release of prostaglandins from blood vessels by vasoactive hormones[50,97-100] suggest that the role of prostaglandins as mediators of antihypertensive mechanisms may result largely from their activity in the vascular wall. Studies of prostaglandins and the mechanisms affecting their release in the vascular wall are necessary in order to understand their role and possible participation in the control of vascular reactivity, because prostaglandin biosynthesis in the vascular wall may represent an intrinsic regulatory mechanism affecting the responses of blood vessels to vasoactive hormones and neurotransmitters in normal and hypertensive stages. A major step toward achieving an integrated concept of prostaglandin mechanisms in vascular tissues has resulted from the studies of Moncada and colleagues,[101] who have discovered that microsomal fractions of several blood vessels are able to synthesize a new arachidonic acid derivative called PGX (or prostacyclin). This material possesses potent platelet antiaggregatory properties as well as being a vasodilator. The same authors[101] have suggested that the antithrombotic mechanism of the vascular wall resides in the ability to synthesize PGX. Deficiency of this prostaglandin may be the initiating event in atherogenesis.

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Renal Kallikrein System, Volemia, and Renal Hypertension

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Plasma, blood, and urine volumes, renal kallikrein, and arterial pressure were measured in control and renal hypertensive rats in order to study the role of the renal kallikrein system in regulating arterial pressure and its relation with the alterations in water handling observed in hypertension. A decrease in kallikrein content of the kidney (157 ± 17 versus 236 ± 16 ng bradykinin equivalents per gram of tissue in control rats) was associated with an increase in plasma volume (38.0 ± 1.6 versus 32.0 ± 0.9 ml/kg body weight in control rats) and an increase in urine volume (45.5 ± 4.9 versus 20.3 ± 1.6 ml/kg body weight per 24 hours in control rats). No linear correlation was found between these factors and the arterial pressure of hypertensive animals. These findings support the hypothesis that changes in renal kallikrein are more directly related to water and electrolyte metabolism than to the arterial pressure regulation. Our results also suggest an interaction between the kallikrein-kinin and the renin-angiotensin-aldosterone systems. The possible relations of both enzymatic systems to the regulation of arterial pressure and of water-electrolyte handling are summarized schematically.

A possible relation between the renal kallikrein-kinin system and hypertension has been postulated.[1] The kallikrein content of the kidney is decreased in some types of experimental hypertension,[2,3] and the amount of urinary kallikrein is markedly lowered in hypertensive animals[4,5] and in patients.[6,7] There is increasing evidence that urinary kallikrein is of renal origin.[8,9]

Bradykinin and kallidin increase water and electrolyte excretion by the kidney.[10] Because alterations in the metabolism of water and electrolytes occur in hypertension, it is possible that variations in renal and urinary kallikrein observed in hypertension are related to changes in water and electrolytes as well as to changes in arterial pressure.

In the present work, plasma, blood, and urine volumes and renal kallikrein were measured simultaneously in control and hypertensive rats in order to study the role of the renal kallikrein-kinin system in arterial hypertension.

MATERIAL AND METHODS

Twenty-four control and 18 hypertensive male Sprague-Dawley rats were used. Rats were maintained on Purina Rat Chow and tap water ad libitum throughout the experiment. Renal hypertension was produced by ligating both poles of the left kidney and removing the right kidney 1 week later.[11] Control animals were subjected to the same procedure, but without ligation of the poles of the kidney.

Arterial pressure was measured indirectly in the tail at weekly intervals. Direct pressure measurements were carried out in the femoral artery under pentobarbital anesthesia at the end of the experiment.

Plasma volume was determined by a dilution technique, using ^{131}I serum albumin. Blood volume was calculated from plasma volume and hematocrit. Kallikrein was obtained from the kidney as previously described[3] and the activity was assayed biologically on isolated rat uterus. Blood urea levels were measured by the urease method.[12]

Table 1.—**Arterial Pressure, Body and Kidney Weights, Plasma Urea, and Hematocrit Values in 24 Control and 18 Hypertensive Rats**

	Control*	Hypertensive*	P
Indirect pressure, mm Hg†	127 ± 3	187 ± 5	<0.0005
Direct mean pressure, mm Hg	138 ± 3	194 ± 4	<0.0005
Body weight, g	441 ± 9	390 ± 17	<0.01
Kidney weight, mg	1,870 ± 40	2,050 ± 90	<0.05
Plasma urea, mg/dl	55 ± 2	66 ± 5	<0.05
Hematocrit, %	47.2 ± 0.5	45.0 ± 1.2	<0.05

*Mean ± standard error.
†Average of the last 2 weeks' values.

RESULTS

Ligating the poles of the left kidney and removing the right kidney increases arterial pressure (Table 1). Rats were considered hypertensive when indirect arterial pressure in the tail was greater than 150 mm Hg for at least 3 weeks and when mean arterial pressure, measured directly in the terminal experiment, was also greater than 150 mm Hg.

Hypertensive rats grew a little more slowly and had slight urea retention but were otherwise in good health. Hematocrit values were slightly lower in hypertensive than in control rats (Table 1).

Urine volume of hypertensive rats that had free access to water was twofold greater than in control animals (Table 2). In control rats, but not in hypertensive animals, urine volume was correlated significantly with indirect arterial pressure values ($r = 0.75$ and $r = 0.22$, respectively).

Plasma volume was significantly increased in hypertensive rats (Table 2) but was not correlated with arterial pressure in either normotensive ($r = 0.14$) or hypertensive ($r = 0.10$) animals. Changes in blood volume followed the changes in plasma volume.

Table 2.—**Diuresis, Plasma and Blood Volumes, and Renal Kallikrein Values in 24 Control and 18 Hypertensive Rats**

	Control*	Hypertensive*	P
24-hour urine volume, ml/kg body weight	20.3 ± 1.6	45.5 ± 4.9	<0.0005
Plasma volume, ml/kg body weight	32.0 ± 0.9	38.0 ± 1.6	<0.0025
Blood volume, ml/kg body weight	60.3 ± 3.2	69.2 ± 2.6	<0.005
Renal kallikrein, ng bradykinin equivalents per gram of tissue	236 ± 16	157 ± 17	<0.0025
Renal kallikrein, ng bradykinin equivalents per total mass	437 ± 29	333 ± 48	<0.05

*Mean ± standard error.

Kallikrein content of the kidney with ligated poles decreased compared to that of the control (Table 2). This decrease was observed both in the medial zone (kidney mass left between ligatures) and in the poles. The biologically assayed values were: 166.6 ± 19.8 (mean ± SE) ng bradykinin equivalents per gram tissue for the medial zone and 121.2 ± 23.2 ng for the poles. These differences were almost significant ($P = 0.10$). The range of values found in the kidney poles was greater than that of the medial zone.

DISCUSSION

Ligating the poles of the left kidney and removing the right kidney produces hypertension associated with expansion of the extracellular space, as indicated by the increase in plasma volume. Urine volume is also modified, confirming the existence of a change in the handling of water in this type of hypertension.

We found a lower total content and a lower concentration of kallikrein in the kidney. This reduction is probably the result of a diminished production of kallikrein by the kidney. Our present data are not conclusive, but the fact that the excretion of urinary kallikrein is very low in this type of hypertension[4] supports this idea.

The decrease in renal kallikrein observed in hypertensive animals can be thought of as directly related to the increase in arterial pressure, but there is also the possibility that it is related to the changes in water and electrolyte metabolism. In our experiments there was a poor correlation between arterial pressure and changes in urine volume in hypertensive rats; this finding differs from the observation in control rats, where a good correlation exists. These observations imply that another factor (or factors) is involved in eliciting the changes in urine volume in hypertension. Our present experiments and the changes observed in kidney and urinary kallikrein activity during hyperhydration and sodium overload,[13,14] without important changes in arterial pressure, suggest that alterations in water and electrolyte metabolism rather than in arterial pressure are most likely associated with variations in kallikrein.

Parallel changes in the renin-angiotensin and the kallikrein-kinin systems have been described after saline infusion, in association with postural changes,[15] and as the result of the reduction in renal blood flow.[16] In renal hypertension produced by ligating the kidney poles, the following changes in the renin-angiotensin system have also been observed:[17] a decrease in juxtaglomerular index as well as in renin content in the medial zone, and a great dispersion in juxtaglomerular index and renin content of the kidney poles. Similar
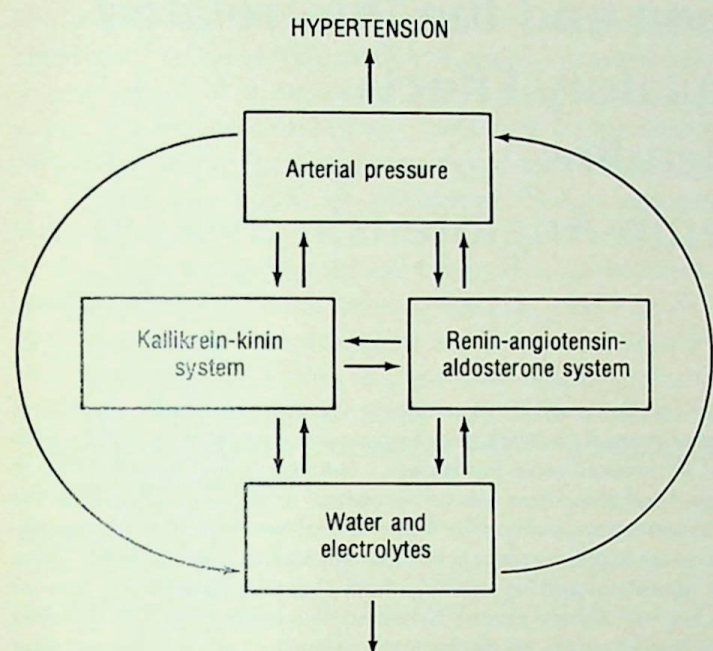
Fig. 1. Interrelations between the kallikrein-kinin and the renin-angiotensin-aldosterone systems and regulation of arterial pressure and water and electrolyte handling by kidney.

findings in the kallikrein content of the kidney were obtained in this work. Finally, the close association between the renin-angiotensin and the kallikrein-kinin systems is reinforced by the fact that the same enzyme[18] converts angiotensin I to angiotensin II (converting enzyme) and inactivates bradykinin (kininase II). The quantity of this enzyme, which is present in plasma, lung, and kidney,[18] is slightly but significantly increased in hypertension induced by ligature of the kidney poles.[17]

A better understanding of renal hypertension requires studies of interactions between the kallikrein-kinin and the renin-angiotensin-aldosterone systems and of their influence on the regulation of arterial pressure and water-electrolyte balance. Figure 1 summarizes the possible relationships. The participation in renal hypertension of two opposite humoral control mechanisms of vascular smooth muscle and of water and electrolyte handling must be considered—the kallikrein-kinin system, which could decrease arterial pressure and facilitate water and electrolyte excretion by the kidney, and the renin-angiotensin-aldosterone system, which could increase arterial pressure and promote retention of water and electrolytes.

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Hypertension and the Interrelated Renal Circulatory Effects of Prostaglandins and the Renin-Angiotensin System

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Blockade of prostaglandin synthesis with indomethacin (1) did not induce significant changes in blood pressure or in renal circulation in renovascular hypertensive rabbits with normal renal blood flow; (2) induced renal insufficiency and aggravated hypertension in hypertensive rabbits whose renal blood flow was below normal levels; (3) did not alter the reversal of renovascular hypertension produced by the release of the renal arterial constriction; and (4) induced a decrease in plasma renin activity by decreasing renin release. These findings indicate that the vasodilator and natriuretic actions of prostaglandins may play an important role in protecting the kidney against ischemia; the facilitating role of renal prostaglandins on renin release raises the possibility that a primary hypersecretion of renal prostaglandins is responsible for Bartter's syndrome, whereas a primary deficiency may be responsible for "low-renin hypertension."

That the vasodilatory effect of prostaglandins may play a major role in protecting several tissues against acute ischemia is shown by the fact that blockade of prostaglandin synthesis effectively prevents the vasodilation of reactive hyperemia in skeletal[1] and cardiac[2] muscle and in the gravid uterus.[3] The notion that this vascular effect was also exerted in the kidney was first proposed by McGiff and associates.[4] This proposal stimulated the studies reported here, which were undertaken to examine the effect of indomethacin-induced blockade of prostaglandin synthesis in some experimental hypertensive states associated with renal ischemia (renovascular hypertension) and during the reversal of renal hypertension induced by release of arterial constriction. In these studies, it was observed that blockade with indomethacin of the synthesis of prostaglandins resulted in a consistent decrease in plasma renin activity. Therefore, other studies were undertaken to define the mechanism of the latter effect.

MATERIAL AND METHODS

The studies were conducted in New Zealand rabbits. Goldblatt hypertension was induced, as in previous studies,[5] by constricting one renal artery without (two-kidney Goldblatt hypertension) and with (one-kidney Goldblatt hypertension) removal of the contralateral kidney. Daily injections of 3 mg/kg of indomethacin suspended in phosphate buffer were given intravenously for 10 days, beginning 30 days after clipping the renal artery. The effect of indomethacin on blood pressure was also studied in a group of normal rabbits that did not undergo operation. Three additional groups of two-kidney Goldblatt hypertensive rabbits, one-kidney Goldblatt hypertensive rabbits, and normal rabbits undergoing the same protocol but treated with phosphate buffer without indomethacin were used as controls.

The effect of blockade of prostaglandin synthesis by indomethacin in reversal of one-kidney Goldblatt hypertension was examined by releasing

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*Established Investigator of the American Heart Association.

the arterial constriction in a group of six rabbits that received 18 mg of indomethacin given intravenously in two doses of 9 mg each, 2 hours apart. Controls consisted of six one-kidney Goldblatt hypertensive animals undergoing a similar protocol and treated with an identical amount of phosphate buffer without indomethacin.

In all of the studies, blood pressure was measured indirectly in the central artery of the ear.[6] Renal blood flow and glomerular filtration rate were measured by the standard clearances of para-aminohippurate and inulin.[7] Plasma renin activity and immunoreactive prostaglandin E-like substances were measured by radioimmunoassay.[8]

RESULTS

Normal Rabbits and Two-Kidney Goldblatt Hypertensive Rabbits With Normal Renal Blood Flow.—The blockade of prostaglandin synthesis by indomethacin in 10 normotensive rabbits (mean blood pressure, 80.3 ± 1.5 mm Hg) and 6 rabbits with two-kidney Goldblatt hypertension (mean blood pressure, 105 ± 2 mm Hg) was followed by a significant decrease in the circulating levels of immunoreactive prostaglandin E-like substance, from 1.15 ± 0.2 ng/ml to 0.2 ± 0.2 ng/ml in normal animals and from 1.0 ± 0.3 ng/ml to 0.2 ± 0.2 ng/ml in hypertensive animals. These changes, however, were not accompanied by any significant changes in renal blood flow (40 ± 2.7 ml/min) or glomerular filtration rate (8 ± 0.5 ml/min). Mean blood pressure levels were not affected.

Two-Kidney and One-Kidney Goldblatt Hypertensive Rabbits With a Renal Blood Flow Below Normal Levels.—In four rabbits the development of two-kidney Goldblatt hypertension was accompanied by a significant decrease in renal blood flow (from 40.1 ± 1.4 ml/min to 26.8 ± 1.8 ml/min, $P<0.01$) and glomerular filtration rate (from 8.5 ± 5.4 ml/min to 5.4 ± 1.0 ml/min, $P<0.05$). Treatment with indomethacin produced renal failure (plasma creatinine increasing to a mean of 7.6 mg/dl), oliguria, and malignant hypertension (mean blood pressure increasing to 168 ± 7.7 mm Hg). None of these four rabbits survived more than 5 days of indomethacin treatment.

Ten rabbits in which the development of one-kidney Goldblatt hypertension (mean blood pressure increasing from 74 ± 2 mm Hg to 102 ± 4 mm Hg, $P<0.01$) was also accompanied by a significant reduction in renal blood flow (38.5 ± 2.5 ml/min to 27.3 ± 1.4 ml/min, $P<0.01$) and glomerular filtration rate (from 7.4 ± 0.4 ml/min to 5.4 ± 0.2 ml/min, $P<0.01$) responded to indomethacin in a similar fashion; that is, there was a further decrease in renal blood flow (to 17.6 ± 3.7 ml/min, $P<0.01$) and glomerular filtration rate (to 3.1 ± 0.7 ml/min, $P<0.01$). Plasma creatinine increased for 0.9 ± 0.04 mg/dl to 3.5 ± 0.8 mg/dl ($P<0.01$), whereas hypertension was severely aggravated and increased from 102 ± 4 mm Hg to 121 ± 6 mm Hg ($P<0.05$). As in other animals, indomethacin induced a decrease in plasma renin activity from 29 ± 1 ng/ml to 3 ± 1 ng/ml per hour ($P<0.01$) and in immunoreactive prostaglandin E-like substance from 2.1 ± 1.3 ng/ml to 0.1 ± 0.04 ng/ml ($P<0.01$). In control animals, the administration of phosphate buffer without indomethacin did not result in any significant change in any of these indices.

Reversal of One-Kidney Goldblatt Hypertension.—The release of the arterial constriction in a group of 10 one-kidney Goldblatt hypertensive rabbits was followed by a complete normalization of blood pressure (from 96 ± 2 mm Hg to 78 ± 1 mm Hg, $P<0.01$) in about 4½ hours. In indomethacin-treated one-kidney Goldblatt hypertensive rabbits, blood pressure also returned to normal levels (98 ± 2 mm Hg to 75 ± 3 mm Hg, $P<0.01$), but the time required to do so, 8 hours, was significantly longer than for the untreated rabbits. In these indomethacin-treated rabbits, prostaglandin synthesis was shown to be completely inhibited in the renal tissue removed after completion of the study and evaluated in vitro.

Mechanism Underlying the Effect of Indomethacin on Plasma Renin Activity.—Studies aimed at further defining the mechansim by which administration of indomethacin produced a decrease in plasma renin activity showed that this was not caused by a decrease in the velocity of the renin-angiotensinogen reaction, because large doses of indomethacin (9 ng/kg) did not change renin substrate levels (from 230.4 ± 15.7 ng/ml to 239 ± 10.3 ng/ml, 6 hours after the injection) or the velocity of angiotensin generation elicited by exogenous renin (5.12 ± 0.29 ng/ml to 5.40 ± 0.36 ng/ml per minute). However, the administration of indomethacin resulted in a significant decrease in a dose-dependent manner, in the release of renin elicited by hemorrhage. Indomethacin also blocked the release of renin elicited by the administration of 5 mg/kg of furosemide.

Furthermore, the administration of other blockers of the prostaglandin synthesis that have a molecular composition different from that of indomethacin (such as meclofenamate and aspirin) was also shown to block renin release. These results indicated that indomethacin lowered plasma renin activity by interfering with renin release and that this action is
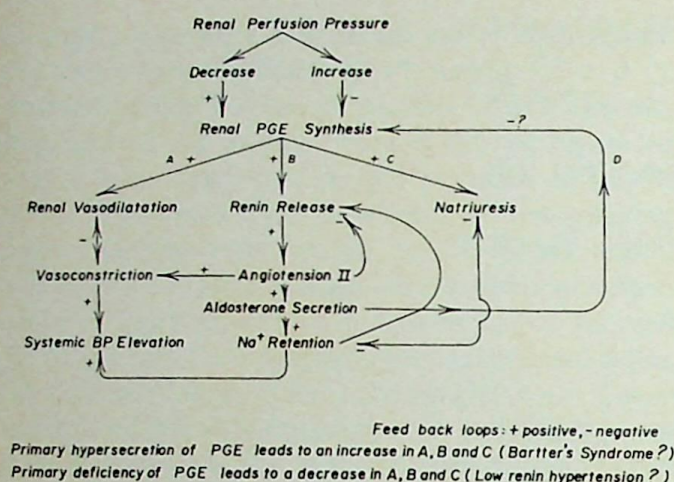
Fig. 1. Hypothetic interactions between renal prostaglandins and renin-angiotensin system within kidney (for details, see Discussion).

most probably mediated through blockade of prostaglandin synthesis.[9]

DISCUSSION

These results suggest that the vasodilator and natriuretic effects of renal prostaglandins are inversely related to renal circulatory function or renal perfusion pressure. A decrease in renal perfusion pressure enhances the synthesis and release of renal prostaglandins. The vasodilator and natriuretic actions of prostaglandin E (Fig. 1 *A* and *C*) can be viewed as a compensatory mechanism to maintain renal circulation and the excretion of salt and water whenever the renal function is compromised by severe ischemia. Suppression of prostaglandin synthesis in animals with a significant reduction in renal blood flow had a deleterious effect, eventuating in renal failure.

These results suggest also that prostaglandins do not play a major role in the maintenance of a *normal* renal function because no significant alterations were observed when prostaglandin synthesis was blocked in animals whose renal circulation was normal.

The activity of the renal prostaglandin system is presumably dampened when renal perfusion pressure is increased above normal (Fig. 1 *upper*), and this may account for our failure to detect any important actions of prostaglandins in the reversal of one-kidney Goldblatt hypertension.

Our studies have also shown that the synthesis of prostaglandins could be an important factor mediating the release of renin (Fig. 1 *B*). It is conceivable that activation of the vasopressor effects of the renin-angiotensin system could not occur in the kidney without the previous stimulation of the prostaglandin system. Such an arrangement would allow the kidney to reset systemic pressure by increasing total peripheral resistance through an increase in angiotensin but without affecting the intrarenal resistance, which would be protected by the counteractions of renal prostaglandins (Fig. 1 *A*). A similar counteracting effect could be exerted by prostaglandins on the sodium-retaining actions of aldosterone. The possibility of this prostaglandin-renin interaction raises the question about the possible inhibitory actions that aldosterone might exert on prostaglandin synthesis as a means of inhibiting the release of prostaglandins and, indirectly, renin (Fig. 1 *D*).

The possibility that renal prostaglandins play a key role in regulation of renal circulatory homeostasis, sodium balance, and renin release is supported by recent observations that the hypersecretion of salt and renin mediated by increased prostaglandin synthesis could account for the manifestations of Bartter's syndrome.[10]

The physiologic consequence of a primary deficiency in synthesis of prostaglandins conceivably could be involved in essential hypertension.[11] Even though such a disturbance has not yet been identified clinically, it might lead to a decrease in plasma renin activity, an increase in intrarenal resistance, and a subtle decrease in sodium excretion with a tendency toward volume expansion, all of which could lead to hypertension of the "low-renin" variety.

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Urinary Kallikrein in Rats Bred for Susceptibility and Resistance to the Hypertensive Effect of Salt and in New Zealand Genetically Hypertensive Rats

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Urinary kallikrein excretion was studied in rats bred for susceptibility and resistance to the hypertensive effect of salt. The rats were on a regular rat chow diet (0.45% sodium content) and tap water and were not hypertensive at the time of the study. Urinary kallikrein excretion, measured by kinin radioimmunoassay, was 10 to 20 times lower in the susceptible rats than in the resistant rats (4.39 ± 1.61 μg/24 hours and 56.4 ± 5.8 μg/24 hours, respectively; $P < 0.001$). Urinary kallikrein excretion was also measured in New Zealand genetically hypertensive rats and in normotensive Wistar-Otago rats (controls). Kallikrein was found to be significantly lower in the genetically hypertensive rats than in the controls (49.1 ± 6.2 μg/24 hours and 76.8 ± 6.9 μg/24 hours, respectively); however, when expressed per 100 g of body weight, there was no significant difference. In conclusion, although urinary kallikrein excretion per rat was decreased in the genetically hypertensive rats when compared with the controls, this difference could be caused by the lower body weight of the genetically hypertensive rats. Urinary kallikrein excretion, when expressed per 100 g of body weight per rat, is significantly lower in susceptible than in resistant rats. This could be a consequence of a genetic defect that may play a role in the development of hypertension, perhaps through alteration of renal function.

In 1962, Dahl and associates[1] established two strains of rats by selective breeding. One strain is salt-susceptible and responds with a significant increase in blood pressure when fed a high-sodium diet; the other is salt-resistant. Using kidney transplants between these two strains, the same investigators have shown that genetically controlled factors operating through the kidney are, in part, responsible for the hypertension.[2-4] Since the susceptible rats only develop hypertension when fed a high-sodium diet, it is reasonable to assume that abnormal renal factors in the kidney are involved in regulating sodium and water excretion. On the other hand, we have postulated that renal kallikrein could be involved in the regulation of sodium and water excretion by the kidney.[5-7] For this reason, we found it of interest to investigate urinary kallikrein excretion in susceptible and in resistant rats. In addition, we also investigated urinary kallikrein excretion in New Zealand genetically hypertensive rats.[8] In these rats, the cause of hypertension is not known; however, it has not been related to the kidney.[9]

MATERIALS AND METHODS

Six salt-susceptible male rats and six salt-resistant rats were placed in individual metabolic cages at 16 weeks of age. All of the rats were kept on a regular sodium diet (0.45% sodium and 0.89% potassium content) and given water ad libitum. Urine was collected, volume was recorded, and aliquots were stored at −20° C for urinary kallikrein, sodium, and potassium determinations. At the end of the collection period, body weight and blood pressure were recorded. Similar procedures were followed with eight genetically hypertensive rats and eight Wistar-Otago control rats at 16 weeks of age.

This investigation was supported in part by a Ford Foundation grant to the Henry Ford Hospital, The Michigan Heart Association, and the American Heart Association.

Urinary kallikrein in the susceptible and resistant rats was measured by using a radioimmunoassay for kinins recently developed in our laboratory.[10] Urinary kallikrein in the genetically hypertensive rats and in the controls was measured by the method described by Marin-Grez and Carretero,[11] slightly modified.[12] The coefficient of correlation between these two methods was 0.77 ($P<0.001$). Urinary kallikrein is expressed in micrograms of kinins generated per minute of incubation per 24-hour urinary volume. Sodium and potassium levels were measured by flame photometry. All values in the text and figures are mean ± SE. Differences between mean values were evaluated by Student's *t* test.
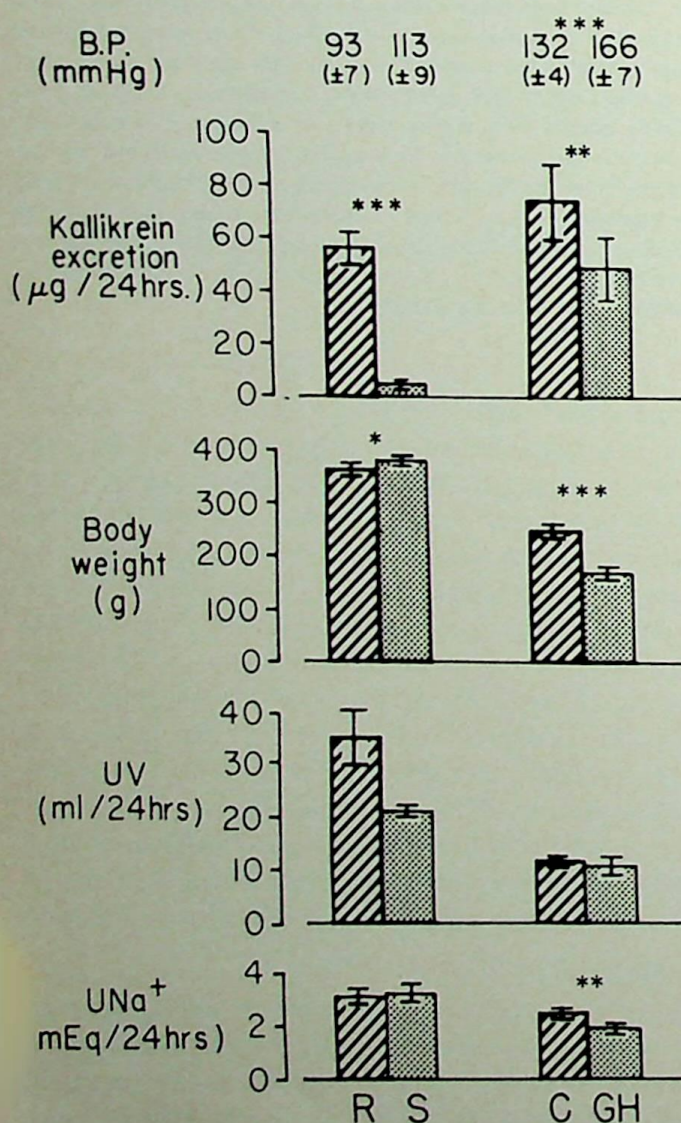
Fig. 1. Blood pressure (*BP*), 24-hour urinary kallikrein excretion, body weight, urinary volume (*UV*), and urinary sodium excretion (UNa^+) in salt-susceptible (*S*) and salt-resistant (*R*), genetically hypertensive (*GH*), and control (*C*) rats. Urinary kallikrein excretion was measured in susceptible and resistant rats for 3 consecutive days and then averaged for each rat; figure shows mean of this average (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

RESULTS

Blood pressure, urinary kallikrein excretion, body weight, urinary volume, and urinary sodium excretion for susceptible, resistant, genetically hypertensive, and Wistar-Otago control rats at 16 weeks of age are shown in Figure 1. Urinary kallikrein excretion per 100 g of body weight was 1.17 ± 0.46 μg/24 hours and 16.09 ± 1.8 μg/24 hours ($P<0.001$), and urinary kallikrein concentration was 0.19 ± 0.07 μg/ml and 2.15 ± 0.59 μg/ml ($P<0.01$), in the susceptible and resistant rats, respectively.

Urinary kallikrein excretion per 100 g of body weight was 28.4 ± 1.8 μg/24 hours and 30.7 ± 2.9 μg/24 hours ($P > 0.05$) in the genetically hypertensive rats and in the controls, respectively.

DISCUSSION

Urinary kallikrein excretion, measured by urinary kininogenase activity, was significantly lower in the susceptible than in the resistant rats. Urinary volume in the susceptible rats was also lower than it was in the resistant rats (22 ± 0.6 ml/24 hours and 35 ± 8.4 ml/24 hours, respectively), but it did not reach statistical significance ($P<0.05$). In the susceptible rats, the fact that urinary kallikrein excretion was 10 to 20 times lower cannot be explained by lower urinary volume, because the concentration of urinary kallikrein per milliliter of urine in the susceptible rats was also significantly lower ($P<0.01$). Blood pressure in the susceptible and resistant rats was similar. The lack of development of hypertension in the susceptible rats was a result of the fact that they were fed a diet containing only 0.45% sodium. These rats had been bred selectively to develop hypertension only when fed a high-sodium diet (8% sodium content). Thus, the conspicuously lower urinary kallikrein excretion in the susceptible rats was not secondary to an increase in blood pressure.

In the genetically hypertensive rats at 16 weeks of age the blood pressure was significantly higher and urinary kallikrein excretion significantly lower than in the Wistar-Otago controls. However, the genetically hypertensive rats weighed significantly less than their controls; and, when kallikrein excretion was expressed per 100 g of body weight, no significant difference was found. In previous work, we have found that urinary kallikrein excretion in genetically hypertensive rats, when measured between 8 and 25 weeks of age and compared with Wistar-Otago controls, was always lower, even before they developed hypertension. Here again, when kallikrein was expressed per 100 g of body weight, no significant difference was found.[13] Further, a significant correla-

tion was found between urinary kallikrein excretion and body weight (r = 0.71). Therefore, it is possible that the decreased urinary kallikrein excretion in the genetically hypertensive rats is a result only of decreased body weight. This is not the case for the susceptible rats, because these rats weighed slightly more than the resistant rats; here, when kallikrein was expressed per 100 g of body weight, the relative differences were increased.

Knudsen and associates,[14] using classic quantitative genetic techniques, have suggested that the expression of two to four genetic loci controls blood pressure responses to sodium in susceptible and resistant rats. One locus, controlling adrenal output of 18-hydroxydeoxycorticosterone (18-OH-DOC), has been identified.[15] The susceptible rats, when compared with the resistant rats, had higher 18-OH-DOC levels in adrenal veins and peripheral plasma.[16] The greater 18-hydroxylase activity in the susceptible rats appears to be offset by a lesser 11β-hydroxylation. This gives rise to characteristic ratios of 18-OH-DOC:corticostersone (B) in the suceptible and resistant rats.[15] The effect of increased 18-OH-DOC and urinary kallikrein excretion is not known, but it seems unlikely that an increase of this mineralocorticoid is the cause of decreased urinary kallikrein excretion, because we have shown that other mineralocorticoids (such as DOC) produce increased excretion of kallikrein.[16] Further, Geller and associates[17] have shown that adrenalectomy produces decreased urinary kallikrein excretion; however, the possibility that this decrease is caused by an alteration of the ratio of 18-OH-DOC:B cannot be ruled out completely. The locus controlling 18-OH-DOC production appears to account for about 16% of the difference in blood pressure between susceptible and resistant strains of rats, with the remaining 84% due to other unidentified genes.[15]

Dahl and associates,[2-4] using interstrain renal transplants, concluded that genetically controlled factors operating through the kidney are, in part, responsible for the hypertension in the susceptible rats. Because the susceptible rats only develop hypertension when fed a high-sodium diet, it is reasonable to assume that at least one of these abnormal renal factors is involved in regulating sodium and water excretion. It may be that one of these loci controls the production of urinary kallikrein. The alteration of this locus could be at the level of the distal tubule, where we have found that urinary kallikrein is produced.[12] Further, it is possible that this is the primary alteration in the kidney and, perhaps, is also the cause of the hypertension. On the basis of our results, however, we cannot exclude the possibility that the decrease in urinary kallikrein excretion in the susceptible rats was secondary to unidentified alterations in the kidney.

In conclusion, although urinary kallikrein per rat was decreased in the genetically hypertensive rats when compared with the Wistar-Otago controls, this difference could be caused by the lower body weight of the genetically hypertensive rats. Urinary kallikrein excretion per 100 g of body weight or per rat is markedly lower in the susceptible rats when compared with the resistant rats. This decrease may be a consequence of a genetic defect that may play a role in the development of hypertension, perhaps through alteration of sodium and water excretion by the kidney.

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END OF SYMPOSIUM

Editorials

PSRO—Are We Getting Our Money's Worth?

Nearly 5 years have passed since enactment of the Social Security amendments of 1972, legislation which included the Professional Standards Review Organization (PSRO) provisions of the law (Section 249F, Public Law 92-603). The declared purpose of Congress was clear. Because of the escalating costs of health care, it was felt that a vehicle was needed that allowed expenditure of federal health care dollars only for care that is necessary and of high quality.

As one sets out on a new program, the methodology of which is experimental, it is considered good scientific practice to evaluate the results from time to time. We might ask, Is it possible to evaluate the results of the PSRO effort to date? Probably it is not.

Though the law states that the Secretary of the Department of Health, Education and Welfare may appoint a third party to perform the duties of a PSRO if physicians in a designated area do not create an effective organization, there is no question that the intent has been for the medical community to assume this responsibility. An innovative and flexible approach was encouraged in the early years. More and more often, however, organizations with contracts to plan conditionally designated PSROs began to receive numerous transmittals from the Department of Health, Education and Welfare, some of which tend to prohibit innovation and flexibility in methodology planning. Some lack of interest in the formation of experimental prototypes was evident on the part of the government.[1] This stage was followed eventually by the recently published notices of proposed rule-making in the Federal Register which outline nearly every step in the review process.[2] Though one may argue that the proposed process is effective, it seems that data are lacking which firmly indicate the value of any process of review at this time.

Responsible physicians support the intent to provide high-quality care at an appropriate level to those who need it and at a reasonable cost. Admission Screening and Continued Stay Review seem to address many of the questions about the need for care and the appropriate level of care. However, these do not touch on the important ingredient of quality, an item of great interest to the physician that might help him provide the best care for those who need it, and to do so in the most appropriate facility. Because of this, the thoughtful physician will perhaps prefer to concentrate on the medical care evaluation study—a retrospective process—so that he might learn how best to deliver care in his own professional setting.

In many situations there appears to be a poor correlation between traditional methods of continuing medical education and the actual delivery of high-quality care at a reasonable cost. This does not imply that traditional continuing medical education is not an important vehicle enabling the physician to become better informed about his particular interest in medicine, but that such educational processes infrequently consider elements of the effective provision of care or the application of knowledge in a prudent and cost-effective manner.[3] A thoughtfully constructed medical care evaluation study, with scientifically selected criteria, that ties the process of care to the patient's outcome would seem to have much to offer.[4]

Although it appears reasonable to carry out admission screening and continued-stay review in order to avoid unnecessary admissions and the use of inappropriate levels of care, more data are urgently needed regarding the cost:benefit ratios of such activities. Recently proposed regulations give a PSRO authority to waive certain elements of admission screening and continued-stay review for providers who have demonstrated prudent practices.[2] This element of determination by physicians must be retained if the cost of review in terms of physician time and monies expended is to be kept at a reasonable level.

It seems likely, with the continued rapid increase of cost of medical care, that the government will become ever more involved,[5] attempting to devise cost-control measures which, themselves, add a great deal to the country's health expenditure. Already, prototypes of ambulatory care review are active. It seems certain that cost-control measures, such as those presently used by PSROs, will be inserted into proposals for national health medical coverage. Because of this, it is urgent that data be gathered so that the presently proposed methods of review can be adequately assessed.

Physician involvement remains important. No one is better qualified to answer the question that asks, What type of cost-containment review and peer evaluation best fits our needs?

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Dr. Hill is President of the Professional Services Quality Council of Minnesota. This is the conditionally designated professional standards review organization for Area III of the state.—Ed.

About The Proceedings

Some Changes; Ad Interspersal; Circulation

A friend of mine, something of a wag, recently informed me that there are only three types of individuals who are entitled to use the plural personal pronoun *we*. "In descending order," he said, "these are royalty, hermaphrodites, and editors." Thus somewhat unflatteringly taxonomized, we take this editorial opportunity to tell our readers about a few changes in *Mayo Clinic Proceedings*.

With this issue we regretfully announce the departure of our very able Executive Editor for the past 8 years, Dr. Charles G. Roland. He returns to his native land to become Jason A. Hannah Professor for the History of Medical and Related Sciences at McMaster University Medical Centre, in Hamilton, Ontario. "Chuck" has always had an interest in the history of medicine, particularly the history of Canadian medicine, and we wish him well in his new venture. We are fortunate to have as his replacement as Executive Editor Dr. Werner Heidel, Head of the Section of Publications here at the Mayo institutions.

Unless you are particularly unobservant, you will have noticed our new cover design this month, the first change in design since the journal went to a larger page size in 1971. We hope you find it as pleasing to the eye as we do. With the change in cover, the mailing wrapper has been discontinued for those copies distributed in the United States but not abroad. If sending the *Proceedings* unprotected through the mails results in excessive damage to your copy, please let us know, for we may need to reassess this cost-saving measure.

Speaking of cost, some, but by no means all, of the very substantial cost of producing and distributing the journal is defrayed by revenue from advertisements of ethical drug companies. Perhaps it is superfluous to point out that acceptance of advertisements does not imply Mayo Clinic endorsement of the advertised products. Some of our readers object to the interspersal of ads throughout the journal, preferring to have these stacked in the front and back of each issue. At least one colleague finds interspersal so annoying that his first act upon receiving a new issue of *Proceedings* is to methodically tear out each interspersed advertising page. Indeed, a recent survey of 765 physicians found that 80% of readers and a slightly higher proportion of authors prefer stacked to interspersed advertisements.[1] We know of no such survey of advertisers or their agents, but most of them seem convinced that interspersal is highly desirable, and they are reluctant to purchase any advertising space unless they get the space they desire. That a few general medical journals continue to have stacked advertisements in the old tradition is a tribute to their affluence and their large subscribing circulation.

With the thought that both some of our readers and some of our advertisers may be overreacting in this regard, we have perforce adopted a policy of limited interspersal. Advertisements are interspersed between some of the articles but never within an article. Advertising pages are numbered separately and may be removed prior to binding the journal, although it is possible, perhaps even likely, that including colorful ads in the bound volume would be of more value to future medical and social historians.

Our circulation continues to grow. Last month's issue of *Mayo Clinic Proceedings* was sent to 65,486 practicing physicians, scientists in fields allied to medicine, medical students, and medical libraries around the world. Of this number over 52,000 copies were distributed in this country—more than 85% of these to individuals. The type of practice of the individual recipients is family practice and general internal medicine, 32%; surgery, including the surgical subspecialties, 18%; and medical subspecialties, 9%; medical students and residents constitute approximately 7% of our domestic readership. More than 13,000 copies were sent abroad to every major country, including 88 copies to the Soviet Union and 84 copies to the People's Republic of China. Several copies each go to such exotic places as Samoa and the Fiji Islands, where your Editor dreams of some day sailing on a slow boat in order to conduct a detailed readership survey. After all, if royalty and others less fortunate can sail away to exotic places, why can't we? Until then, we shall try to keep you abreast of significant developments in medicine as perceived from the Mayo Clinic. If you have some particular needs or desires or complaints in this regard, feel free to let us know.

J.L.J.

1. Key JD, Sholtz KJ, Roland CG: Unpublished data

Book Reviews

The Criminal Personality, Volume I, by Samuel Yochelson and Stanton E. Samenow, 538 pp, $25, New York: Jason Aronson, 1976

This is the first of three volumes entitled *The Criminal Personality*. The second and third have not yet been published. This volume presents a detailed description of criminal thinking and action patterns. The authors state, "Volume 2 will present new procedures for achieving change in the criminal in which choice and will (redefined) have been combined with an operational, phenomenological approach." At the very end of the 530 pages the authors also state, "To have written Volume 1 without Volume 2 would have been only to engage in an academic enterprise for the classroom. The concepts in Volume 1 are validated by the results achieved in the change process described in Volume 2." This reviewer agrees heartily with the first of these statements: reading this first volume is only an academic enterprise. Application in practice is the only valid proof of theory, and nowhere does that appear in this volume.

What does appear is an account of over 14 years of study and work with criminals at St. Elizabeth's Hospital in Washington, D.C. This is elucidated at great length in describing the thought and action patterns of those subjects. As such, the work is thorough and infinitely detailed.

In the first chapter, entitled "The Reluctant Converts," the authors recount their frustration in trying to work with their subjects by conventional psychoanalytic techniques. They then changed to nonanalytic but conventional techniques with equal frustration. It was not until they arrived at their own techniques (described only in the presently unavailable Volume 2) that they had success.

The second chapter is a review of all the existing theories of criminal behavior. These include organic and biologic theories and controversies, sociologic and economic theories, and, finally psychoanalytic theories. The authors have done their homework, but they reject each of these approaches. They also reject most psychologic test data on the grounds that the criminal quickly learns how to manipulate these instruments to his own use. They seem to adhere most closely to the theories of Cleckley[1] regarding the psychopathic personality.

In the past, no single theory has seemed very useful in the attempt to modify severe and repetitive antisocial behavior. The authors promise to prove the efficacy of their theory in Volume 2. Everybody else may be wrong and the authors may be right, but this volume does not convince.

The index is inadequate, the quality of paper poor, and there are numerous proofreading errors.

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1. Cleckley HM: The Mask of Sanity. Fourth edition. St. Louis, CV Mosby Company, 1964

Broncho-pulmonary Immunopathology, by Claude Molina, 251 pp, with illus, $29.50, New York: Churchill Livingstone, 1976

There is little doubt that the most rapidly expanding category of respiratory diseases in the past decade has been that of the immunologically mediated lung diseases. It is difficult for the physician with a particular interest in this field to be fully conversant with the latest developments. Some of the entities, such as pigeon breeder's disease and bagassosis, would be of only academic interest to the majority. However, it is becoming increasingly clear that a considerable number of patients who have recurrent pneumonitis or chronic pulmonary fibrosis may have their diseases as a result of continual inhalation of antigenic substances within their homes or at work. For example, contamination of air conditioners and humidifiers by certain molds may cause hypersensitivity pneumonitis and even chronic fibrosis.

Unfortunately, the precise pathogenesis of many of the pulmonary disorders that are believed to be immunologically mediated is far from clear. Indeed, different authors investigating these disorders find quite conflicting results, particularly in reference to serologic data. It is therefore timely to have this book on bronchopulmonary immunopathology available for reference. Molina provides a comprehensive review of the spectrum of immunologically mediated lung diseases. The introductory section describes the characteristics of the specific immune reactions as well as to the immunodeficiency syndromes. These are concise but of sufficient depth to give a sound basis in understanding immunologic mechanisms. Particular attention is directed in this section toward the unique features of the lung in modifying these mechanisms. The second and third parts provide descriptions of specific entities ranging from bronchial asthma to hypersensitivity pneumonitis to pulmonary malignancy. Analyses of the disorders include the histopathologic, physiologic, biochemical, and even molecular biological changes.

Although the field contains confusing and conflicting data, this book makes definite progress in untangling the pathogenesis of many of the diseases. Thus, it would be a valuable addition to the bookshelves of any physician concerned with pulmonary diseases. There is one major drawback to the book, however. The original edition was published in French in 1973 and the English version in 1976. I could find no reference in the book later than 1972. Since that time, new entities and new immunologic mechanisms have been described. Despite that drawback, the book remains an important contribution to the overall subject.

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Atlas of Pediatric Diseases by Helmut Mol and Walter Kleindienst, 275 pp, with illus, $39.50, Philadelphia: W. B. Saunders Company, 1976

This atlas is a remarkable collection of pediatric disorders displayed by beautiful colored photographs that have been reproduced with astonishing clarity. The product is a valuable quick reference for students and residents in pediatrics or family practice.

The table of contents lists an impressive assemblance of birth defects, trauma, infectious and acquired diseases, diseases affecting various systems, and iatrogenic afflictions. Each clinical entity is presented under the headings of definition, clinical findings, differential diagnosis, and treatment. On the facing page are two to four photographs and, where appropriate, tables, charts, graphs, or reproductions of roentgenograms are also used.

There are criticisms that should be made, however. For example, in numerous instances the therapy recommended is at variance with our approach at this institution. Antibiotics are recommended for whooping cough, steroids are recommended for anaphylactoid purpura, and bed rest is recommended for acute glomerulonephritis. For the treatment of funnel chest, the authors suggest that an arrest of the progression of the deformity might be brought about by exercise, although surgery is recommended for severe forms. Therapy for psoriasis is stated to be corticosteroids and antimetabolites. In addition, there are many terms used in this book that are not common in this country, including the following: phlegmon, dystrophy, intoxication, toxicosis, subtoxic dyspepsia, disturbed micturition (for obstructive uropathy), and parulis (for dental abscess).

Correction of the above defects in subsequent editions would make this a most valuable book that certainly would serve as a handy reference for pediatric or family practice residents as well as for student clerks serving in an outpatient department or emergency room.

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Psychosomatic Medicine: Its Clinical Applications, edited by Eric D. Wittkower and Hector Warnes, 350 pp, with illus, $19.95, Hagerstown: Harper & Row, 1977

The two distinguished editors of this remarkable book have selected an international group of contributors — psychiatrists and internists — who are each expert in a particular area of psychosomatic medicine. The book is divided into four parts containing a total of 32 chapters.

Part one is introductory and describes basic principles of management, crisis intervention, and the process of consultation in psychosomatic medicine. The material is presented in such a way as to make it comprehensible to every medical practitioner.

Part two discusses models of intervention for particular conditions such as chronic pain and hemodialysis

Part three, somewhat loosely entitled "Psychotherapies," includes chapters on such therapeutic approaches as group psychotherapy, hypnosis, behavior therapy, autogenic therapy, biofeedback, pharmacotherapy, Morita therapy, and yoga. Thirteen chapters in this part adequately serve the purpose of acquainting the practitioner with most of the commonly used modalities of therapy for psychosomatic illness.

Part four, on specific disorders, contains 12 chapters, each of which deals with psychosomatic aspects of illness involving an organ system and includes chapters on psychosomatic disorders in children and in older persons.

This is an immensely informative book for its size. The brevity of the chapters is compensated for by an extensive bibliography following each chapter. The book is made more readable by the frequent use of brief and cogent case histories. This is not a book for the expert on psychosomatic medicine. It is intended for the rest of us. It is difficult to imagine a book that could be more highly recommended to the average practitioner, no matter what his specialty, who cares for and about each person who comes seeking many different things in the role of a patient.

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Recent Advances in Gastroenterology, No. 3, edited by Ian A. D. Bouchier, 348 pp, with illus, $32.50, New York: Churchill Livingstone, 1976

The purpose of this book was to describe new developments "in physiology, biochemistry and pathology which have a direct bearing on patient care." Therefore, it is primarily directed toward clinicians, internists, pediatricians, gastroenterologists, and surgeons, who care for patients with gastrointestinal diseases. The choice of subjects was conditioned "by those fields of particular growth . . . and an attempt to reflect as many interests as possible." The subjects included were physiology of the gastroesophageal junction and hiatus hernia, fat absorption, hormone-secreting tumors of the gastrointestinal tract, the effects of massive small bowel resection, connective tissue disorders affecting the GI tract, the use and abuse of laxatives, alcohol and the GI tract, endoscopic cannulation of the papilla of Vater, clinical aspects of bile acid metabolism, shunts for hepatic disease, liver disease in infants and children, and cystic fibrosis of the pancreas.

I thoroughly enjoyed reading this book. It is a multiauthored text written by experts from Great Britain and the United States but the quality of writing and style are rather uniform. Most of the chapters are sparkling examples of clarity and contain up-to-date information and references. In particular, the chapters entitled "Alcohol and the Gastrointestinal Tract" and "The Use and Abuse of Laxatives" were particularly well written.

Although the book contains only 348 pages (a positive feature, in my opinion) and is expensive, the fund of information it contains is exemplary and I would recommend it to those desiring a compact review of current topics in gastroenterology.

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BOOK NOTICES

Food: The Gift of Osiris, volume 1, by William J. Darby, Paul Ghalioungui, and Louis Grivetti, 528 pp, with illus, $27, New York: Academic Press, 1977

If we can know what foods a given people ate and what foods they rejected, we can infer much about their lives, their religion, their medicine, and many other factors. In this volume the authors present a scholarly study of the food of ancient Egypt that provides an important contribution to our knowledge of the history of that country. The illustrations are superb.

The Faces of Eve: Women in the Nineteenth Century American Novel, by Judith Fryer, 304 pp, with illus, $11.95, New York: Oxford University Press, 1976

In analyzing a large number of 19th century American fictional heroines, the author finds four broad patterns: the Temptress, the American Princess, the Great Mother, and the New Woman. These stereotypes display the beliefs of the various authors and reflect general opinions on the roles of women—thus providing a valuable insight into more recent cultural changes in these roles. Generous quotes illuminate the author's thesis.

Medical Botany: Plants Affecting Man's Health, by Walter H. Lewis, and Memory P. F. Elvin-Lewis, 533 pp, with illus, $27.50, New York: John Wiley & Sons, 1977

Although we tend to think of modern drugs as being synthetic products, many natural agents are in regular use throughout the world. This book attempts to provide historical, pharmacologic, and clinical information about medicinal plants in three extremely broad categories—injurious, remedial, and psychoactive. These data are available in no other single source.

Influenza: The Last Great Plague. An Unfinished Story of Discovery, by W. I. B. Beveridge, 136 pp, with illus, $4.95, London: Heinemann, 1977

Because of the large number of facts presented crisply and clearly in the impeccable style that characterized the author's chief opus, *The Art of Scientific Investigation*, this slim book is a model of informative readability. The history of influenza, milestones of viral research, and a cogent summary of our present knowledge all are here; and the book can be read in about an hour.

Discovery Processes in Modern Biology: People and Processes in Biological Discovery, edited by W. R. Klemm, 352 pp, with illus, no price listed, Huntington, New York: Robert E. Krieger Publishing Company, 1977

The editor has persuaded 13 practicing North and South American scientists to write autobiographical remarks, stressing their scientific careers. Each account is prefaced by a portrait and a listing of personal data about the author and by an editor's introduction. The autobiographical notes are intriguing and generally well written; scientists who participated included Mauricio Rocha e Silva, Jean Mayer, and Hans Selye. The book helps dispel the entrenched myth that science is an impersonal and objective profession.

Grants: How To Find Out About Them and What To Do Next, by Virginia P. White, 366 pp, $19.50, New York: Plenum Press, 1976

Here is a book that tells you how to find out about grants, who to apply to for grants for various purposes, and how to prepare your application. Granting sources described are both governmental and private. Unfortunately, the index is weak; nevertheless, this book is the best single source of this kind of information that is currently available.

Walter C. Alvarez: American Man of Medicine, by David H. Scott, 380 pp, $8.95, New York: Van Nostrand Reinhold Company, 1977

Here are compiled a selection of Alvarez's editorials from *Modern Medicine*, published in the 1960's and 1970's. The range of subjects is broad—from "Meeting the Demand for Corpses" to dying of fright. The style is breezy and readable; there are no references.

Legacies in Ethics and Medicine, edited by Chester R. Burns, 332 pp, $7.95, New York: Science History Publications, 1977

Legacies in Law and Medicine, edited by Chester R. Burns, 316 pp, $7.95, New York: Science History Publications, 1977

Together, these volumes provide a carefully contrived selection of readings in medical history. With the exception of material from the editor's pen, all of these essays have been published previously in scholarly periodicals and books. In these days of inflation it is pleasing to be able to comment favorably on the price of books; these are remarkably inexpensive, a fact that will make them truly available to students, the intended audience.

To Be an Invalid: The Illness of Charles Darwin, by Ralph Colp, Jr., 299 pp, with illus, $15, Chicago: The University of Chicago Press, 1977

Darwin's ill health, which dominated most of his adult years, has been the source of much speculation. Numerous and varied hypotheses have been formed. We will, of course, never have a definitive diagnosis. But Colp presents a convincing case suggesting that Darwin was incapacitated by "psychophysiologic" disorders to which he had a predilection throughout his life and which were exaggerated by his concerns about the public and scientific reception of his evolutionary theories. Much previously unpublished material shores up Colp's hypothesis.

Issues and Ideas in America, edited by Benjamin J. Taylor and Thurman J. White, 390 pp, with illus, $19.95, Norman: University of Oklahoma Press, 1976

The editors have gathered contributions that comprise a particularly effective bicentennial volume. Essay topics include a historiography of Negro slavery, ecology since 1900, the growth of scientific medicine, and American history as experiment. The general caliber of the writing is scholarly but readable. Illustrations would have enhanced some of the presentations but are almost totally absent.

Scientific Quotations: The Harvest of a Quiet Eye, by Alan L. Mackay and Maurice Ebison, 204 pp, with illus, $14, New York: Crane, Russak & Company, 1977

Someone else's choice quotations always omit one's own favorites, but this lack is more than offset by discovering many totally new aphorisms (e.g., Camus: An intellectual is someone whose mind watches itself) and anecdotes (e.g., T. H. Huxley: If only I could break my leg, what a lot of scientific work I could do). Unfortunately, many of these quotations are given faulty, misleading, secondary, or no citations.

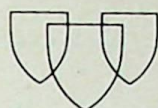
Pioneer to the Past: The Story of James Henry Breasted, Archaeologist, by Charles Breasted, 426 pp, $5.95, Chicago: The University of Chicago Press, 1977

The first professional Egyptologist in North America, Breasted is best known to physicians for his translation of the Edwin Smith Surgical Papyrus. But this effort was a small portion of the immense scholarly production of James Breasted, much of that production being carried out in penurious circumstances. Finally, his accomplishments gave him access to Rockefeller Foundation and other funds, one fruit of which was the Oriental Institute of the University of Chicago, at which school Breasted pursued his entire career.

The History of Psychotherapy: From Healing Magic to Encounter, edited by Jan Ehrenwald, 589 pp, $20, New York: Jason Aronson, 1976

Man, says the editor, is the most important therapeutic agent for man. This eclectic selection of writings illumines the growth of our knowledge into what we now call psychotherapy. The Yellow Emperor, Sir Kenelm Digby, Freud, and Fritz Perls represent just a small portion of the cast of characters; the range in time is from 2500 BC to 1976. There is reading here to fascinate any member of the health professions, especially those who deal with patients regularly.

American Folk Medicine: A Symposium, edited by Wayland D. Hand, 355 pp, with illus, $12.95, Berkeley: University of California Press, 1976

The "Old Hag" tradition of Newfoundland, the role of animals in infant feeding, and the use of American Indian foods as medicine are a sampling of the contents of this fascinating book. It is the product of a symposium held in Los Angeles and presents, with scholarly aplomb, information on various aspects of folk medicine, some of them in evidence today. Quite apart from their dramatic interest, these accounts also emphasize the importance—and the general neglect—of studies of folk medicine as part of medical history.

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Allergic Granulomatosis and Angiitis (Churg-Strauss Syndrome)

Report and Analysis of 30 Cases

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The clinical and morphologic findings of allergic granulomatosis and angiitis of Churg and Strauss in 21 men and 9 women were reviewed. The classic features are those of systemic vasculitis in a setting of bronchial asthma and eosinophilia. Pathologically there is necrotizing vasculitis of small arteries and veins with extravascular granulomas, and infiltration of vessels and perivascular tissues with eosinophilia. These features differentiate it from polyarteritis nodosa. The lungs, peripheral nerves, and skin are most frequently involved. Renal failure was encountered in only one patient in this series. Shortness of the interval from onset of asthma to appearance of vasculitis is an unfavorable prognostic sign. Corticosteroids seem to influence long-term survival favorably.

When polyarteritis nodosa was first described, more than a century ago, it seemed a fairly definite entity.[1] As information accumulated, however, it became clear that many cases identified as polyarteritis nodosa had features that differed from the classic clinical and pathologic findings.[2-6]

In 1951, Churg and Strauss[7] reported a study of 14 cases (11 by autopsy) of a form of disseminated necrotizing vasculitis occurring exclusively among asthmatics; fever, hypereosinophilia, and a fulminating fatal illness involving multiple organ systems were associated with a distinctive microscopic pattern of necrotizing arteritis, eosinophilic infiltration, and extravascular granulomas.

In 1957, Rose and Spencer[8] reported 111 autopsy cases of polyarteritis nodosa and distinguished among these 32 cases having pulmonary involvement with features similar to those described by Churg and Strauss.

Since the publication of those two articles, there have been but a few reports[9-15] of solitary cases with the clinical and the pathologic findings now referred to as Churg-Strauss syndrome.

CASE MATERIAL

We present herein a clinical and pathologic analysis of 30 cases of allergic granulomatosis and angiitis of Churg and Strauss diagnosed in patients at the Mayo Clinic between 1950 and 1974.

Cases were sought in which bronchial asthma was accompanied by systemic vasculitis that differed from polyarteritis nodosa, as detailed

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Table 1.—**Churg-Strauss Syndrome: Histopathology in 30 Cases**

Necrotizing extravascular granulomatosis	22
Necrotizing vasculitis of small arteries and veins	30
Prominent eosinophilia of vessels and perivascular tissues; accompanying lymphocytes, plasma cells, some histiocytes	30
Fibrinoid necrosis of vessel walls	12

below. The 30 selected for study included 21 men and 9 women, whose ages ranged from 15 to 69 years, averaging 47. Morphologic studies included 39 biopsies: 17 of muscle, 9 of skin, 2 of bronchus, 2 of bowel, 1 of testis, 2 of lung, 3 of nose, 2 of prostate, and 1 of liver. All yielded evidence of the pathology described below. All original sections of tissue were reviewed, and additional sections were made when needed. All autopsy material available (six cases) was reviewed. Tissue stains included hematoxylin-eosin, elastic van Gieson, and Movat. The histopathologic findings are summarized in Table 1. In 22 cases, typical histopathology was seen, including necrotizing extravascular granulomas and necrotizing vasculitis of small arteries and veins. In the other eight, only necrotizing vasculitis of small arteries and veins was identified, without extravascular granulomas. The necrotizing vasculitis in all cases was characterized by prominent eosinophilic infiltration of vessels and
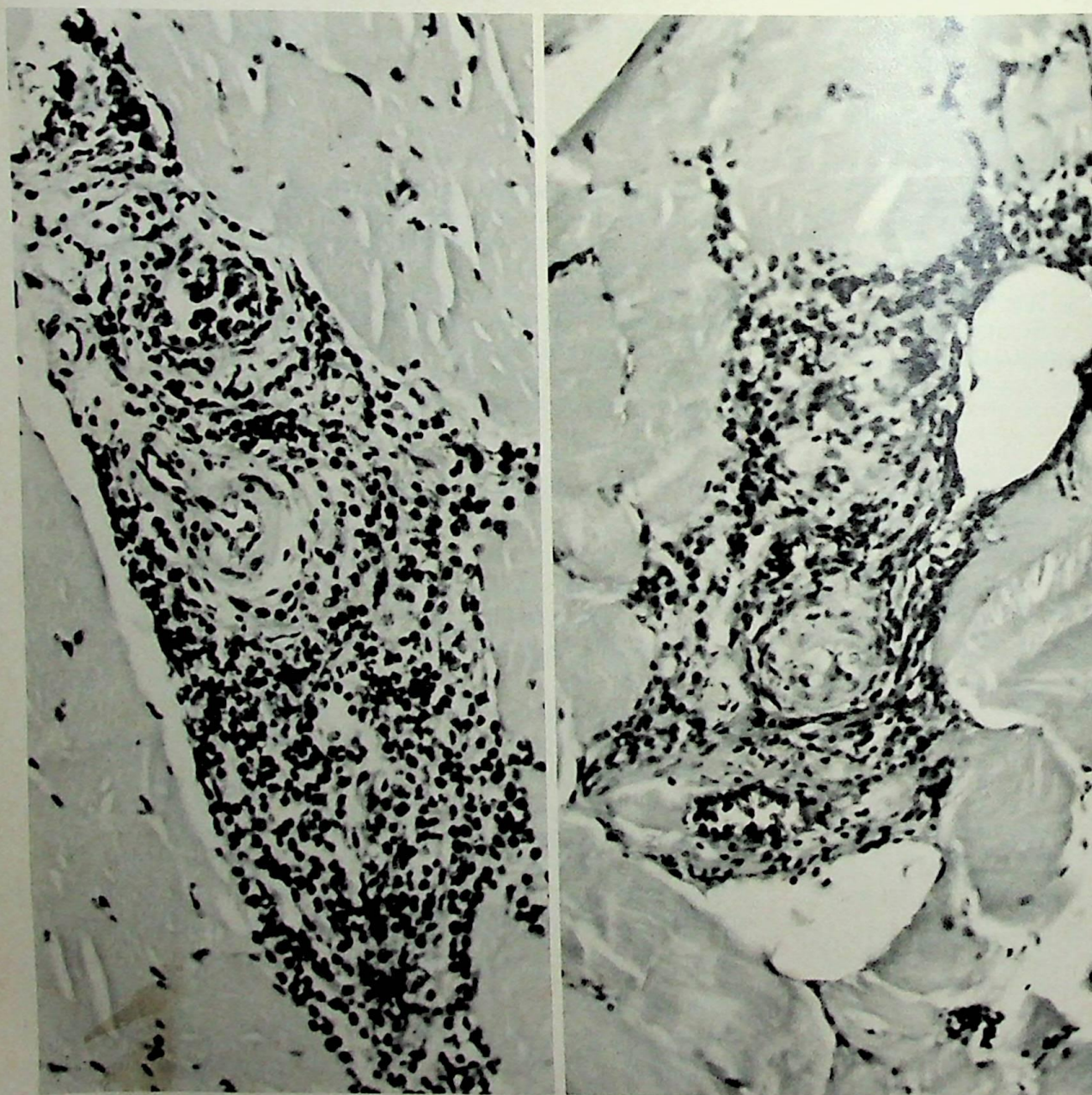
Fig. 1. Early, active lesions involving vessels and stroma. *Left,* Muscle-biopsy section showing early vasculitis of small intermuscular artery and vein with adjacent infiltrate composed primarily of eosinophils and some mononuclear cells in developing allergic granuloma. (Hematoxylin and eosin; ×160.) *Right,* Muscle-biopsy section showing early vasculitis of small intermuscular artery and vein with histiocytic aggregation in developing allergic granuloma. (Hematoxylin and eosin; ×160.)
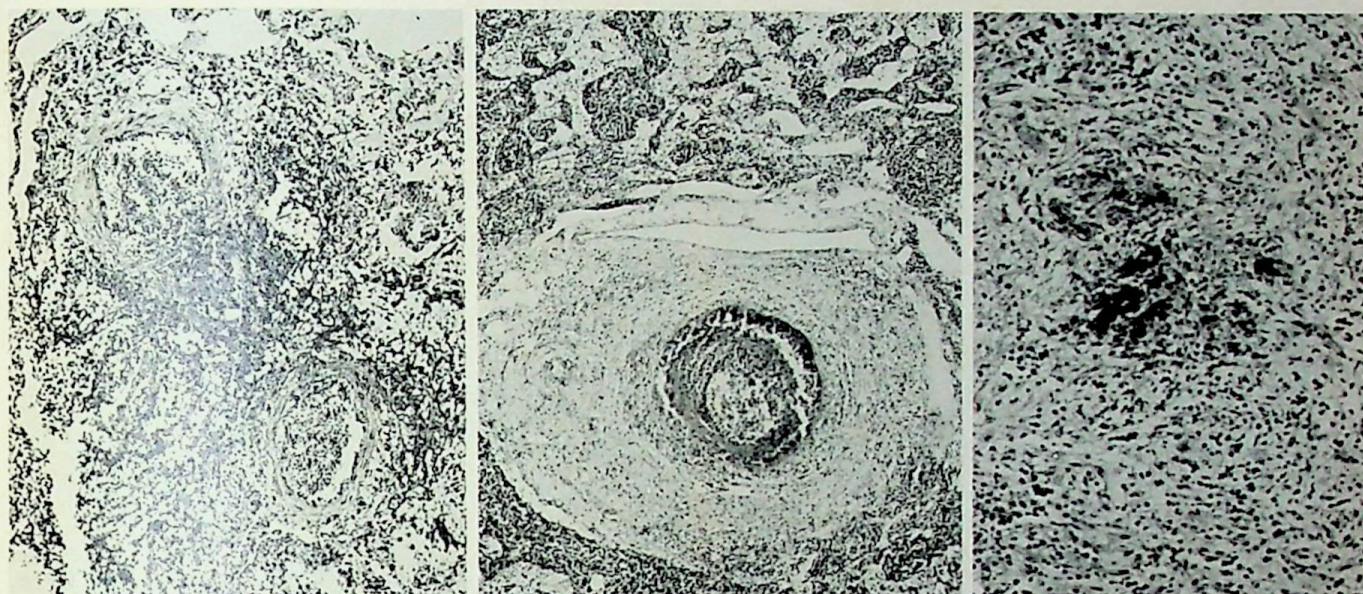
Fig. 2. Well-established, active necrotizing and occlusive lesions. *Left,* Autopsy section of lung showing necrotizing granuloma with fibrinoid central area involving intervascular stroma and vessel walls, all surrounded predominantly by eosinophils. (Hematoxylin and eosin; ×100.) (From Kelalis PP, Harrison EG Jr, Greene LF: Allergic granulomas of the prostate in asthmatics. JAMA 188:963-967, 1964. By permission of American Medical Association.) *Middle,* Section of meso-appendiceal lymph node showing transmural necrotizing vasculitis with loose fibrotic tissue containing scattered eosinophils and mononuclear cells. Mural thrombus partially occludes lumen of vessel. (Hematoxylin and eosin; ×65.) *Right,* Biopsy section of penis, showing fibrinoid necrotic zone of allergic granuloma around small vessel with surrounding eosinophils and loose fibrosis. (Hematoxylin and eosin; ×160.)

perivascular tissues, with accompanying lymphocytes, plasma cells, and some histiocytes. Fibrinoid necrosis of vessel walls was noted in 12 cases. The course of the disease is manifested in successive morphologic patterns of its lesions—from early and active (Fig. 1) to well-established, active, and necrotizing (Fig. 2 and 3) to late chronic healing and occlusive (Fig. 4).

Clinical and Laboratory Features.—The mean duration of asthma in this series was 8 years. It began at the same time as the manifestation of systemic vasculitis in six cases, but preceded it in all others. One patient had asthma that had begun more than 30 years prior to the onset of vasculitis. Allergic rhinitis occurred in 21 patients. Most patients had fever at some point in their clinical course. Anemia and weight loss were common, as was leukocytosis and an elevation of the erythrocyte sedimentation rate. Peripheral eosinophilia was seen at some time in each case, and in one instance eosinophils amounted to 81% of the peripheral leukocyte count. It appeared that the degree of eosinophilia and the erythrocyte sedimentation rate were good indicators of activity of the disease. Two patients had elevations of serum immunoglobulin E (IgE).

FINDINGS

Systemic Involvement.—Chest roentgenography revealed abnormalities in 8 of the 30 cases. These ranged from transient patchy pneumonic infiltrates (Fig. 5) to massive bilateral nodular infiltrates without cavitation (Fig. 6) or to diffuse interstitial disease (Fig. 7). Some lesions remained stable after an initial period of improvement, and some stabilized without improvement. Occasionally, complete regression of a rather widespread active pulmonary process was seen during treatment with corticosteroids. Frequently, asthmatic symptoms receded as evidence of necrotizing vasculitis became prominent. This interesting clinical feature deserves emphasis.

Five patients had significant episodes of abdominal pain, the cause of which could not be established. One patient had gastric ulceration and another had pseudopolyp formation of the colon consistent with chronic ulcerative colitis. In neither patient was histologic confirmation available. Three patients underwent laparotomy. One had allergic granulomas involving the stomach, liver, and omentum. Another had an allergic granulomatous process massively involving the ascending colon, originally thought to be due to carcinoma. The fifth patient died of perforation of the small bowel with peritonitis and septicemia due to necrotizing granulomatous vasculitis and allergic granuloma of the small bowel.

Twenty patients had cutaneous manifestations, which varied in form from tender, nodular, subcutaneous lesions (in 8 cases) to petechial or purpuric (non-
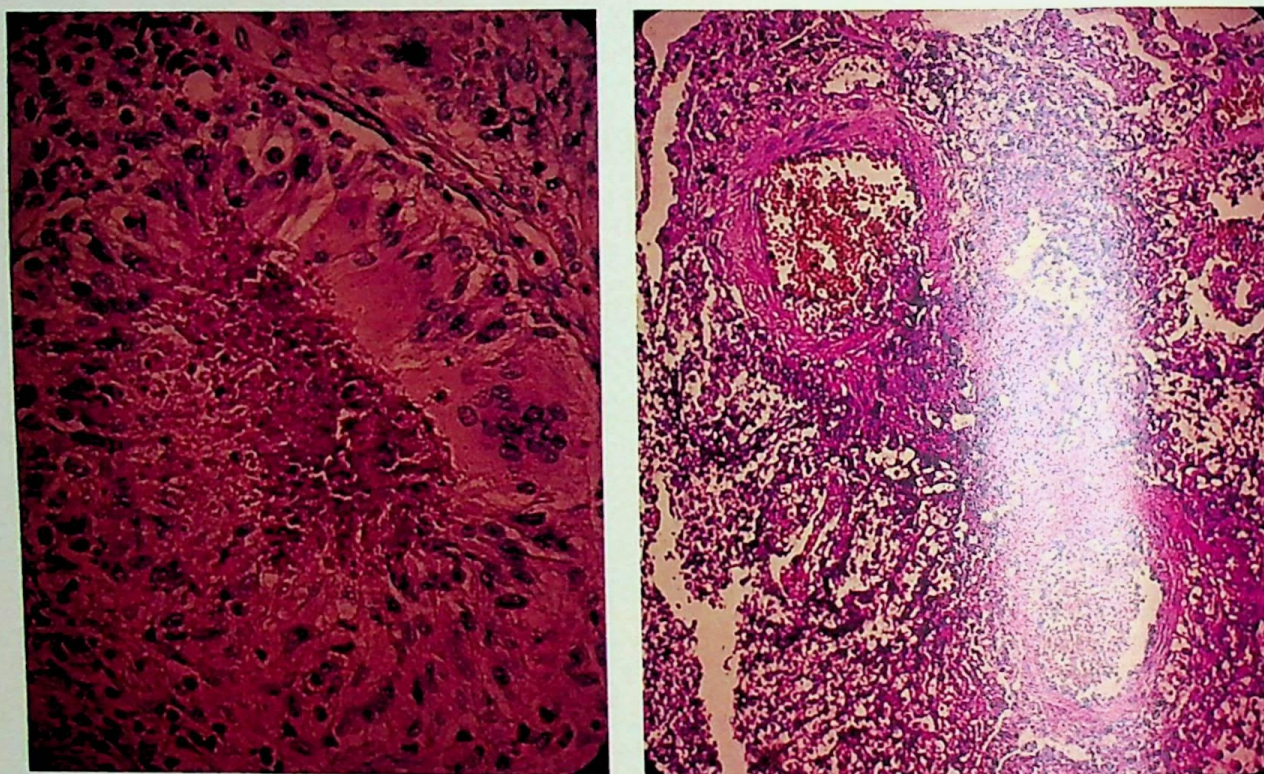
Fig. 3. *Left* (same case as in Fig. 2 *left*), Biopsy section of prostate, showing characteristic well-established, active allergic granuloma with central annular zone of eosinophilic fibrinoid necrosis surrounded by palisading epithelioid histiocytes and abundant eosinophils. (Hematoxylin and eosin; ×250.) (From Kelalis PP, Harrison EG Jr, Greene LF: Allergic granulomas of the prostate in asthmatics. JAMA 188:963-967, 1964. By permission of American Medical Association.) *Right,* Section from intranasal biopsy showing necrotizing allergic granuloma with central fibrinoid necrosis having border of scattered epithelioid histiocytes and occasional giant cell, imitating infectious granuloma. Eosinophils are prominent in adjacent submucosa. (Hematoxylin and eosin; ×160.)

thrombocytopenic) lesions. Four had cutaneous infarcts. One had an allergic granuloma of the penis, a feature not previously reported in this syndrome. Marginal ulceration of the cornea was seen in one instance. Neurologic involvement was seen in 19 of our patients, manifested usually as mononeuritis multiplex.

Renal disease was not prominent in our series. Only one patient had renal failure. Death occurred at home; and so far as we know, autopsy was not performed. Six patients had microscopic hematuria without erythrocyte casts, and three had slight elevations of the serum creatinine or urea. No instance of focal necrotizing glomerulitis was seen in the six autopsy cases, and no renal biopsies were performed.

A feature seen in three of our patients, but not described by Churg and Strauss, was allergic granulomatosis of the prostate and lower urinary tract. In one case (reported in detail elsewhere[16]), the illness began with acute urinary retention. Digital examination of the prostate revealed it to be moderately enlarged, hard, and tender; pathologic examination showed typical allergic granulomas. Another patient (also described elsewhere[17]) had allergic granulomas of the prostate, penis, and both ureters which caused obstructive uropathy, hydronephrosis, and atrophy of the renal cortex bilaterally. In both of these patients, pulmonary involvement later became prominent roentgenographically. Conversely, in a third case, allergic granulomas of the prostate developed 7 years after resolution of an extensive pulmonary process. The importance of a urologic history and careful digital examination of the prostate in providing early clinical data for a quick diagnosis is evident from these cases. None of the women in our series had gynecologic symptoms or signs.

Six patients had significant joint symptoms during their illness, usually in the form of migratory polyarthralgias. Two patients had evidence of active synovitis with effusion. Seven of 10 patients tested for rheumatoid factor had positive results, usually of low titer. Two of these patients had titers of 1:2,560 and 1:20,480—the latter in the case of rheumatoid arthritis which was considered clinically inactive.

Treatment, Course, and Follow-Up.—In our series, 27 patients were given corticosteroid therapy. This was usually begun when biopsy disclosed evidence of vasculitis after signs of widespread organ involvement
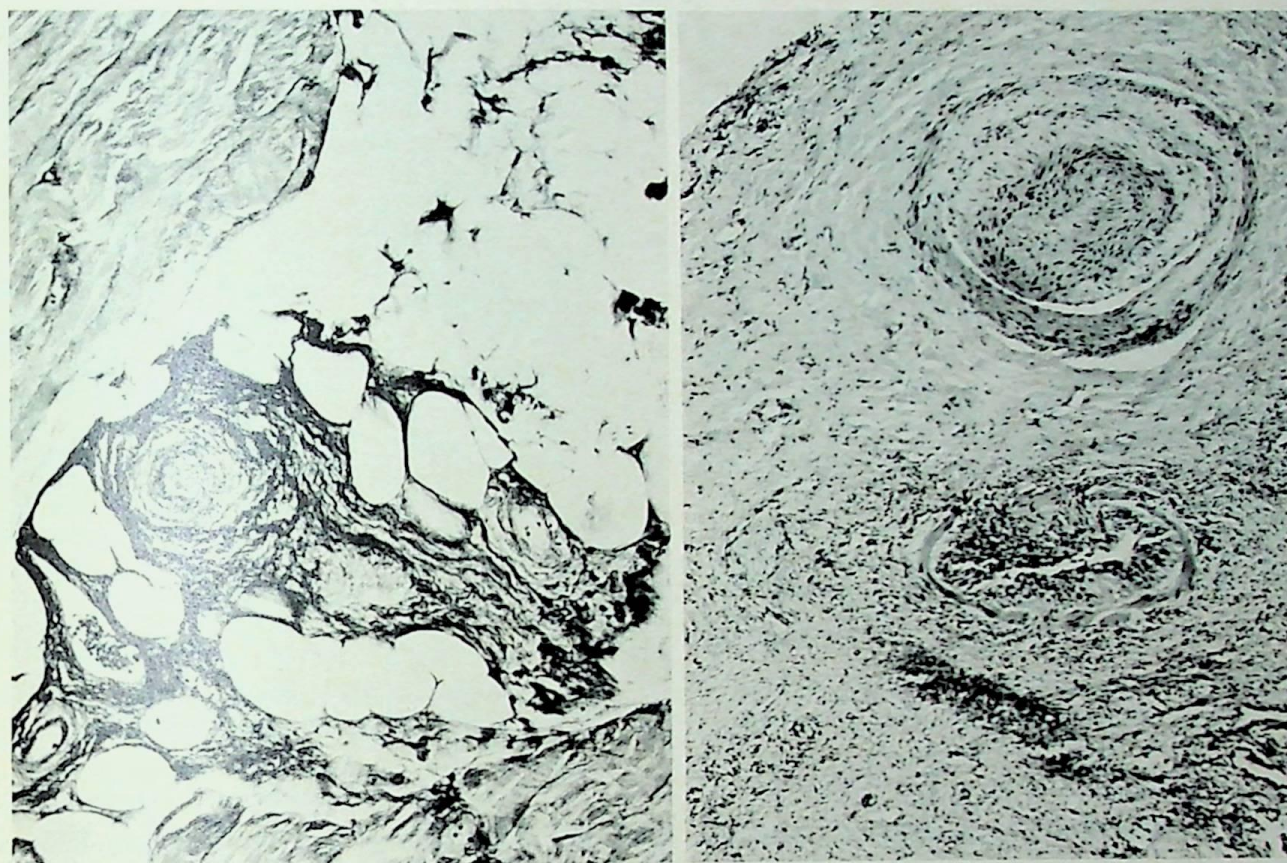
Fig. 4. Late healing and occlusive lesions. *Left,* Muscle-biopsy section showing fibrous occlusion of small artery and vein. Note defect in arterial elastica due to healed necrotizing vasculitis. (Elastic van Gieson stain; ×160.) *Right* (same case as in Fig. 2 *right*), Biopsy section of lung showing fibrous occlusion of lumen of medium-sized artery (above) with perivascular fibrosis. Focal, residual, active allergic granuloma is in stroma (below) adjacent to partially obliterated small bronchus. (Hematoxylin and eosin; ×100.)

had appeared clinically. However, a few of the 27 had received steroids previously for severe bronchial asthma; and a small number were receiving long-term corticosteroid therapy, albeit in the stage of intermittent maintenance, when they developed evidence of active Churg-Strauss angiitis. In some cases the stigmata of hypercortisonism were evident on physical examination at a time when it seemed necessary to raise the level of corticosteroid therapy. From 40 to 60 mg of prednisone or its equivalent were given daily until evidence of response appeared; and then the amount was tapered as clinical circumstances permitted. Occasionally, from 100 to 120 mg daily of prednisone was required. Cyclophosphamide was administered late in the fulminating course of one patient who died. Azathioprine therapy was followed by excellent clinical improvement in one case. Of course no conclusions can be drawn from only two instances; but it is worth noting that similar agents have shown promise in treatment for other forms of necrotizing vasculitis, particularly Wegener's granulomatosis. One patient died of widespread salmonella infection 1 year after the onset of his disease. Long-term corticosteroid therapy could have been instrumental in this unfortunate complication. Of the survivors, several have permanent residua from their peripheral neuropathy and some continue to show evidence of a chronic pulmonary process roentgenographically.

Follow-up was achieved in all 30 cases. Though the mean duration of asthma prior to onset of vasculitis was 8 years in the series as a whole (30 years in 1 case), it was only 3.1 years among the 15 patients who have died. This difference suggests that shortness of duration from onset of asthma to onset of vasculitis is an unfavorable prognostic sign. Of the 15 deaths (Table 2), 3 occurred within a year after the symptoms of vasculitis appeared. The interval from onset of signs and symptoms of vasculitis to death ranged from 6 months to 15 years, averaging 4.6 years.

The survivorship curve for all patients in the study is shown in Figure 8. It is significantly lower than the curve for expected survivorship. The parallelism beyond 5 years suggests that late survivorship in Churg-Strauss syndrome is fairly normal, but the number of cases in that period is not sufficient to
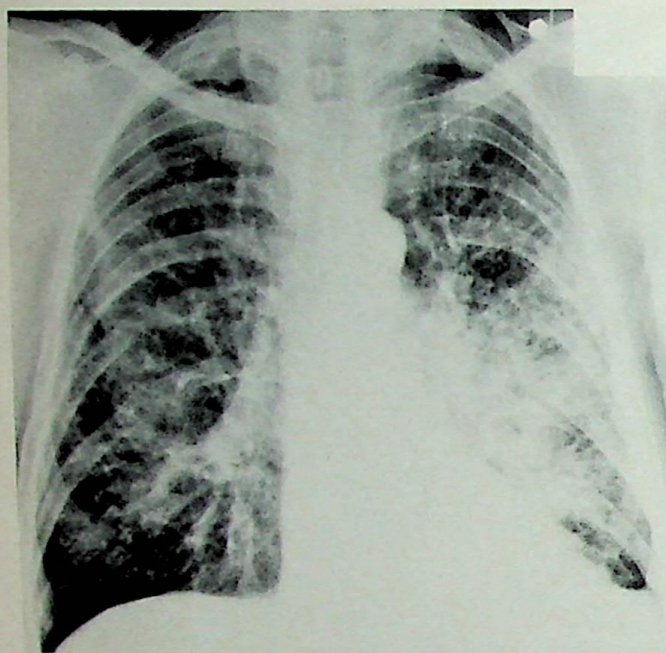
Fig. 5. Roentgenographic demonstration of localized infiltrate in left lower lobe of patient with Churg-Strauss syndrome originally thought to be Löffler's syndrome.
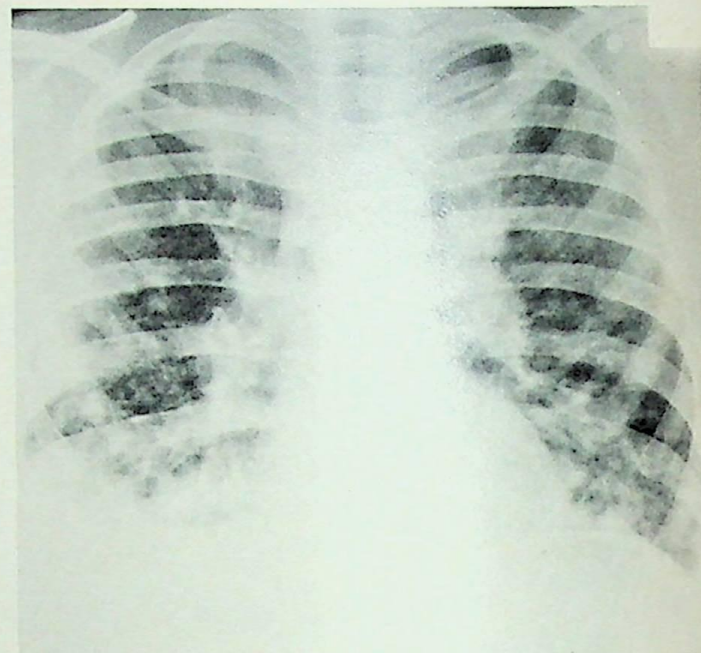
Fig. 6. Roentgenographic demonstration of nodular pneumonic infiltrate in patient with Churg-Strauss syndrome.

validate the appearance. Survival of 1 year was achieved by 90% of the patients, 3 years by 76%, and 5 years by 62%. The median survival now is more than 9 years, and two patients have survived more than 20 years.

COMMENT

Differential Diagnosis.—Classic polyarteritis nodosa is perhaps the entity most likely to be confused with Churg-Strauss syndrome, because of the presence of asthma in both entities. Reports of the incidence of asthma with polyarteritis nodosa have ranged from 4% to as high as 54%.[18] Microscopically, polyarteritis nodosa affects small and medium-sized arteries, whereas Churg-Strauss syndrome affects small arteries and small veins. The predominant cellular infiltrate in polyarteritis nodosa is the neutrophilic leukocyte, but in Churg-Strauss syndrome it is the eosinophil. Necrotizing extravascular granulomas are not seen with polyarteritis nodosa. Whereas asthma is the rule in Churg-Strauss syndrome, it is infrequently seen in polyarteritis nodosa.

Wegener's granulomatosis, like Churg-Strauss syndrome, usually produces a combination of necrotizing granuloma with other vascular lesions. These similarities may cause confusion. Churg[19] has reviewed this problem in detail. A history of allergy is typical in Churg-Strauss syndrome, whereas in Wegener's granulomatosis a background of allergy is no more frequent than in the general population. Initial clinical findings in Churg-Strauss syndrome relate to asthma, whereas ulceration and necrosis in the respiratory system are typical of Wegener's granulomatosis. Eosinophilia, only an occasional and minimal finding in Wegener's granulomatosis, is prominent in Churg-Strauss syndrome. Histologically, the coagulative or liquefactive necrotizing epithelioid granuloma in Wegener's granulomatosis differs morphologically from the more fibrin-
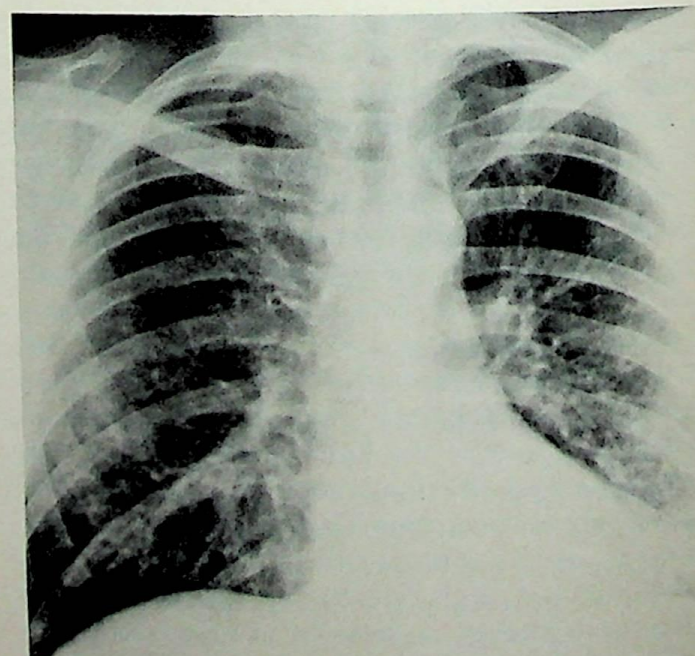
Fig. 7 (same case as in Fig. 2 *middle*). Roentgenographic demonstration of diffuse interstitial pattern in patient with Churg-Strauss syndrome.
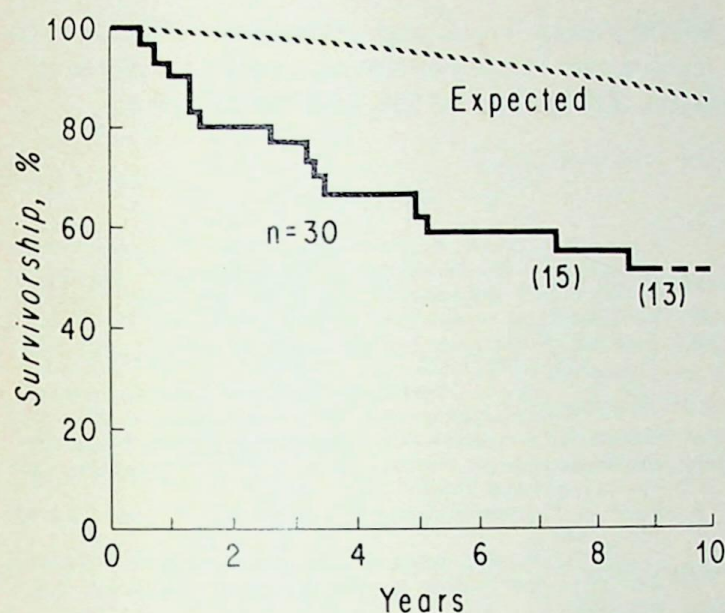
Fig. 8. Estimated survivorship (actuarial method) among 30 patients with allergic granulomatosis and angiitis (Churg-Strauss syndrome), dating from first appearance of signs and symptoms of vasculitis; and expected survivorship (broken line). Numbers in parentheses represent patients living and under observation at years of follow-up indicated.

oid necrotizing (allergic) epithelioid and eosinophilic granuloma seen in the Churg-Strauss syndrome. Wegener's granulomatosis is characterized by a predilection of the granulomas for the upper and lower respiratory tract; but in Churg-Strauss syndrome, involvement of the upper airway with vasculitis is infrequent. Both conditions are characterized by multisystem necrotizing vasculitis, but in Wegener's granulomatosis focal necrotizing glomerulitis is common and the most frequent cause of death is renal failure, whereas renal disease has been uncommon in our experience with Churg-Strauss syndrome.

Löffler's syndrome, characterized by transient shifting pulmonary infiltrates associated with peripheral eosinophilia and often with asthma, was the first clinical manifestation in several of our cases. Chronic eosinophilic pneumonia presents a somewhat different clinical course: asthma is not universal, being absent from three of nine patients studied by Carrington and associates.[20] Peripheral eosinophilia is inconstant, and the chest roentgenogram is distinguished by the so-called photographic negative appearance. Systemic vasculitis is not a clinical feature of this condition. Lung biopsy reveals interstitial infiltration of eosinophils, plasma cells, and histiocytes, with intra-alveolar eosinophils and fibrinous exudation. Whereas small areas of vasculitis may be seen in the lung, this is not a prominent pathologic finding.

Table 2.—**Churg-Strauss Syndrome: Proximate Cause of Death in 15 Cases**

Cause	No. of cases
Myocardial infarction	3
Congestive heart failure	2
Status asthmaticus	1
Salmonella septicemia	1
Ruptured aortic aneurysm	1
Renal failure	1
Bronchopneumonia	1
Small-bowel perforation, peritonitis	1
Unknown causes	4

Anaphylactoid or Henoch-Schoenlein purpura, seen in children and young adults, is characterized by angiitis (usually acute) and abdominal and joint pains and acute nephritis. It usually is of self-limited course, and bronchial asthma is absent.

Allergic bronchopulmonary aspergillosis resembles Churg-Strauss syndrome when there are eosinophilia, asthma, and pulmonary infiltration. However, this specific diagnosis should be made readily on the basis of culture of the organism from the bronchial tree, together with appropriate serologic tests for precipitating antibody or an Arthus reaction on skin testing. We are unaware of any instance of allergic granulomatosis and angiitis arising out of this entity.

Comparisons With Experience of Others.—The clinicopathologic pattern derived from our series is similar to that originally described by Churg and Strauss, lending weight to the validity of their syndrome as a distinct entity. Although biopsy revealed no extravascular granulomas in eight of our patients, the presence of intense eosinophilia in tissues and peripheral blood, in the setting of asthma and vasculitis, compelled us to include these patients. Additionally, the absence of granulomas in these cases may have been due to adverse sampling. The low frequency of renal pathology in our series differs from that reported by Churg and Strauss and is not readily explicable.

Vasculitides that involve the respiratory tract seem to differ from those that do not. Granulomatous changes are seen frequently with the former and infrequently with the latter. Wilson and Alexander[18] reported that when polyarteritis was associated with asthma, peripheral eosinophilia of high magnitude was found in more than 90% of patients. Conversely, only 6% of patients without asthma had peripheral eosinophilia, and that was not of great magnitude. Two of our patients had increased levels of IgE. Un-

fortunately, this test was either not available or not ordered in the other cases. Similarly, increased levels of IgE had been reported in Wegener's granulomatosis. Conn and associates[21] found immunologic differences between patients with and without vasculitis involving the lungs. In general, they found that without lung involvement there was a greater frequency of rheumatoid factor and immune complexes and decreased serum complement. Eosinophilia and elevated IgE levels were more often associated with lung involvement. Balancing this report, however, is that of DeRemee and associates,[22] who found rheumatoid factor in 15 of 35 patients with Wegener's granulomatosis. This finding correlated strongly with the presence of glomerulitis. No tests for immune complexes were performed in that series.

Perhaps the lung may have a unique part in the pathogenesis of systemic vasculitis. The presence of eosinophilia in both tissue and peripheral blood, together with asthma—putatively on an allergic basis—and with increased IgE in the blood, suggests that the immediate hypersensitivity system is intimately involved in the pathogenesis of Churg-Strauss syndrome. Although elevation of IgE in patients with Wegener's granulomatosis suggests a similar process, the absence of peripheral and tissue eosinophilia implies a dissociation of function of these allergic markers.

From prognostic and therapeutic standpoints, the separation of Churg-Strauss syndrome from the other vasculitides, particularly Wegener's granulomatosis, is valuable. Whereas Wegener's granulomatosis often requires treatment with cytotoxic agents, particularly in the presence of renal disease, it appears that corticosteroids are sufficient in the case of Churg-Strauss syndrome, at least as reflected by the data in our series. Survival in our series contrasts strikingly with that reported by Rose and Spencer,[8] for whose patients corticosteroids were not available. In their series, 50% had died by 3 months after onset of vasculitis and only one survived 5 years. From this, it appears that corticosteroid therapy reduces the lethal effects of vasculitis, though infrequency of major renal involvement in our patients also may have some part in the achievement of this favorable response.

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Juvenile Nephronophthisis and Medullary Cystic Disease

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Juvenile nephronophthisis and medullary cystic disease are morphologically indistinguishable hereditary renal disorders. These diseases have been described independently but very likely are a single disease entity and occur as a juvenile-onset, autosomal recessive form and as an adult-onset, autosomal dominant form. We agree with this hypothesis and present here the clinical, laboratory, and pathologic findings of six cases of the juvenile-onset, autosomal recessive form, along with an analysis of the mode of transmission of these and other published cases of the disorder.

Juvenile nephronophthisis or medullary cystic disease of the kidney is a hereditary disease characterized by polyuria and polydipsia, decreased renal concentrating ability, anemia, and eventual renal failure.[1] Skeletal changes and the growth retardation typifying chronic renal disease are usually present in affected children. These changes are hereafter referred to as renal osteodystrophy.[2,3]

The absence of urinary abnormalities, other than decreased concentrating ability, characterizes this disease process.[1] Hypertension is unusual, though found more commonly in adults and often found in the late stages of the disease.[4-6]

It is the purpose of this paper to describe our experience with six children from four kindreds with juvenile nephronophthisis. About 150 patients have been reported so far, with the largest series reported by Habib.[7]

SUMMARY OF OUR CASES

Records of six children with nephronophthisis or medullary cystic disease who were seen at the Mayo Clinic during the period 1961 to 1968 were reviewed. A hospital in another state made available the records of an affected sibling of one patient.

Clinical Findings (Table 1).—The symptom that brought three of the six patients to medical attention was difficulty walking because of pain or deformity of the legs. All six patients had polyuria and polydipsia beginning between the ages of 2 and 6½ years, but walking difficulties were not noticed until 12 to 16½ years of age. Pallor and unexplained anemia were also early but usually ignored symptoms. There were no other congenital anomalies such as have been reported frequently in other cases of medullary cystic disease and nephronophthisis.[3,8-13]

Findings on physical examination varied with the stage of disease in which the patient was first seen. One child, who was examined because of the presence of the disease in a sibling, had no positive findings at the time of the initial examination but later manifested clinical and laboratory evidence of the disorder.

In four children, height was below the third percentile for age at the time of the initial examination. A fifth patient showed evidence of growth failure during the observation period. Genu valgum was seen in four patients initially and developed later in one additional patient. Blood

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Table 1.—**Historical and Clinical Findings**

Family	Patient, sex	Chief complaints	Age, yr		Height, % for age	Weight, % for age	Poly-uria	Poly-dipsia	Genu valgum	Survival from admission date
			At onset	At admission						
A	1, M	Pallor, difficulty walking, pain in feet and ankles	11 4/12	12	3	25	+	+	+	6 mo
A	2*, F	Examination due to brother's illness		10	25	25	+	+	−	Still living
B	3†, M	Knock-knees, pain in legs, tiredness	12 1/2	13	3	3	+	+	+	2 yr 0 mo
B	4†, F	Pallor, tiredness, poor appetite		10 1/2	3	3	+	+	+	4 yr 0 mo
C	5, M	Difficulty walking, painful knock-knees	16 9/12	17 3/12	3		+	+	+	2 mo
D	6*, F	Polyuria, polydipsia, anorexia	6 1/2	8 3/12	3	3	+	+	+	8 yr 2 mo

*Patient had renal transplantation.
†A detailed study of the calcium and phosphorus metabolism of these patients was published previously.[2]

pressure was normal in all patients except for two children who developed hypertension terminally.

Roentgenologic Findings.—Roentgenographic examination showed signs of renal osteodystrophy in five patients. The outlined kidney appeared small in all patients who were in advanced stages of the disease.

Laboratory Findings (Table 2).—Laboratory evidence of decreased renal function varied with the stage of disease in which the patient was first seen. All patients except one had elevated serum creatinine levels. Their anemia progressed with the severity of the renal insufficiency. Evidence of salt wasting was noted in one patient.

Urinalysis showed a specific gravity of 1.012 or less in all patients. One patient, seen for strabismus at the age of 22 months, had a urinary specific gravity of 1.012 at that time, although his serum creatinine and hemoglobin were normal. He did not present with symptoms related to decreased renal function until 12 years of age.

Minimal proteinuria (grade 1 or 2 on a 1 to 4 scale) was found in all six patients. Three patients had minimal erythrocyturia (grade 1 or 2). Leukocytes (grade 1 or 2) were found in the urine of five patients.

Renal clearance determinations in two patients showed PAH clearances proportionately much lower than inulin clearances. In other words, the filtration fraction was high. One patient with a more nearly normal filtration fraction was in an early stage of the disease. She had polyuria and polydipsia but no azotemia or renal osteodystrophy.

Three patients who had renal osteodystrophy eventually were found to have elevated serum alkaline phosphatase values.

Course.—Five of the six patients have died. Four are known to have died in renal failure.

The fifth patient died several years after receiving a kidney transplant from her mother. After surgery, her serum creatinine decreased to normal levels, her urine specific gravity increased to 1.013, and her serum alkaline phosphatase level decreased. How-

Table 2.—**Laboratory Findings**

Family	Patient, sex	Serum urea, mg/dl	Serum creatinine, mg/dl	Hemoglobin, g/dl	Serum alkaline phosphatase, U/liter	Creatinine clearance, ml/min	Urinary specific gravity
A	1*, M	318	7.8	8.7		8.21	1.004-1.008
A	2, F	43	0.95	12.9	111	75	1.011
B	3*†, M	146	4.9	8.0	50		1.002
B	4*†, F	166	4.8	5.9	16.6		1.005
C	5*, M	372	13.4	6.8	81	2.6	1.006
D	6*, F	146	2.5	9.4	25.1	17	1.003

*Bone roentgenography showed renal osteodystrophy.
†A detailed study of the calcium and phosphorus metabolism of these patients was published previously.[2]

Fig. 1. Cut surface of one kidney from patient with juvenile nephronophthisis shows multiple cysts of medulla.

ever, there was a later gradual decrease in renal function. She did not return for further observation and died several years later at home. Information concerning the cause of her death has been unavailable.

The only patient still alive when this report was prepared had received a kidney for transplantation from her father. The surgery was done elsewhere. After transplantation, she did well for 4 years but then developed signs and symptoms of an acute transplant rejection. Her serum creatinine has remained at 2.0 to 2.5 mg/dl since that episode. A renal biopsy done at the time of the rejection reaction revealed severe interstitial and perivascular round-cell infiltrates but no evidence that the kidney was affected by nephronophthisis.[14]

Pathologic Findings.—On gross morphologic examination of specimens from three patients, the kidneys were small and had fine to coarsely granular surfaces, thinned cortexes, and indistinct corticomedullary junctions. Cysts measuring less than 1 mm up to 1 cm in diameter were observed in the medulla, most frequently near the corticomedullary junction (Fig. 1). The calyces and pelvis appeared normal.

Microscopically, medullary cysts were seen in three of four cases, usually near the corticomedullary junction (Fig. 2). The largest measured 2 mm. They were lined by flattened cuboidal epithelium similar to the epithelium of collecting ducts (Fig. 3). Many of the cysts contained granular, eosinophilic, proteinaceous material similar to material also found in tubular lumens and in dilated Bowman's spaces (Fig. 1). Communication between the cysts and collecting ducts or between the cysts and the ascending or descending loops of Henle was not observed.

The glomeruli were markedly decreased in number and had varying degrees of hyalinization, concentric periglomerular fibrosis, and thickening of the capsular basement membrane (Fig. 4). Cellularity was normal and capillary basement membranes were not thickened primarily. Numerous glomeruli had cystic dilatation of Bowman's space with compression of the capillary tuft. In some instances, the tuft was absent in the dilated spaces. Granular eosinophilic material was often present within the dilated spaces.

Tubules with varying degrees of atrophy, hypertrophy, tortuosity, and dilatation were observed (Fig. 5). There was an eosinophilic, granular, proteinaceous material partially occluding some tubular lumens. Calcium was observed in the lumens in one case. Tubular basement membranes were thickened and showed splitting with reduplication. Collars of connective tissue surrounded most atrophic tubules.

Particularly notable were the thickened basement membranes and prominent dilatation of the ascending and descending limbs of the loop of Henle. These changes were also distinctive in the collecting ducts. Dilatation of some collecting ducts was so extreme as to make the areas appear cystlike. In one case, the epithelial cells of the collecting ducts were vacuolated.
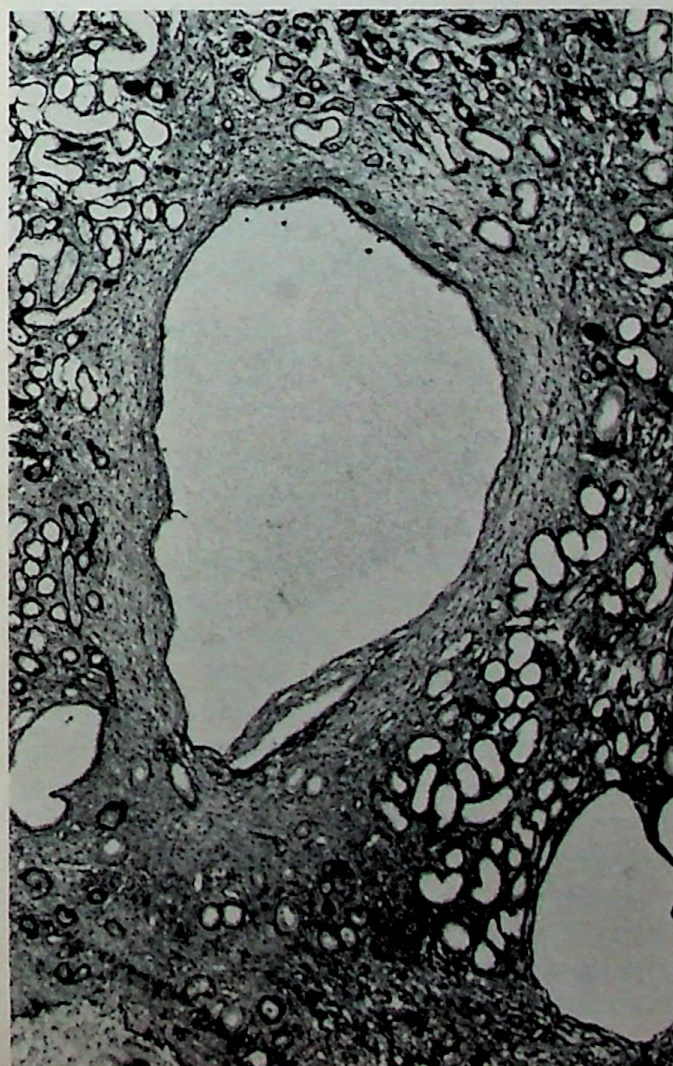
Fig. 2 Section of renal medulla showing variability of cyst size. (Periodic acid-Schiff; ×40.)

Fig. 3. Photomicrograph of cyst wall showing flattened cuboidal epithelial lining. Thickening of tubular basement membranes is also prominent. (Hematoxylin and eosin; ×500.)

There was a diffuse increase in interstitial fibrous connective tissue with a mononuclear infiltrate that was primarily lymphocytic (Fig. 3). The interlobular and arcuate arteries showed minimal intimal fibrous thickening. There was no arterial hyalinization.

Cystic, glomerular, tubular, and interstitial changes were consistent with those in reported cases. Though we did not observe communications between cysts and other medullary structures, others have found connections of cysts with tubules or collecting ducts, or both.[9,15-17] Ivemark and associates noted cystlike dilatations of the flexure of the loop of Henle.[18,19]

Genetic Findings.—Our patients represented four kindreds. In none of the families was there any history of consanguinity or of renal disease in parents or other relatives. In one family with two children, both were affected. In the other families, two of eight siblings, two of five siblings, and three of four siblings were affected. The ratio of affected males to affected females was 5:4. The ratio of affected siblings to unaffected siblings was 1:2 if the proband in each family was excluded.

DISCUSSION

One hundred fifty cases of nephronophthisis and medullary cystic disease have been reported, with the largest series (50 patients) reported by Habib.[7]

Histologic findings in nephronophthisis and medullary cystic disease are identical. They include cysts of the medulla, predominantly near the corticomedullary junction, and hyalinization of glomeruli. Tubules exhibit varying degrees of atrophy, hypertrophy, tortuosity, dilatation, and thickening of basement membranes. There is a diffuse interstitial mononuclear infiltrate. The pathogenesis is unknown and there is no successful therapy for the progressive renal failure other than renal transplantation.

There has been much debate over differentiation between the two disorders. The authors of most of the
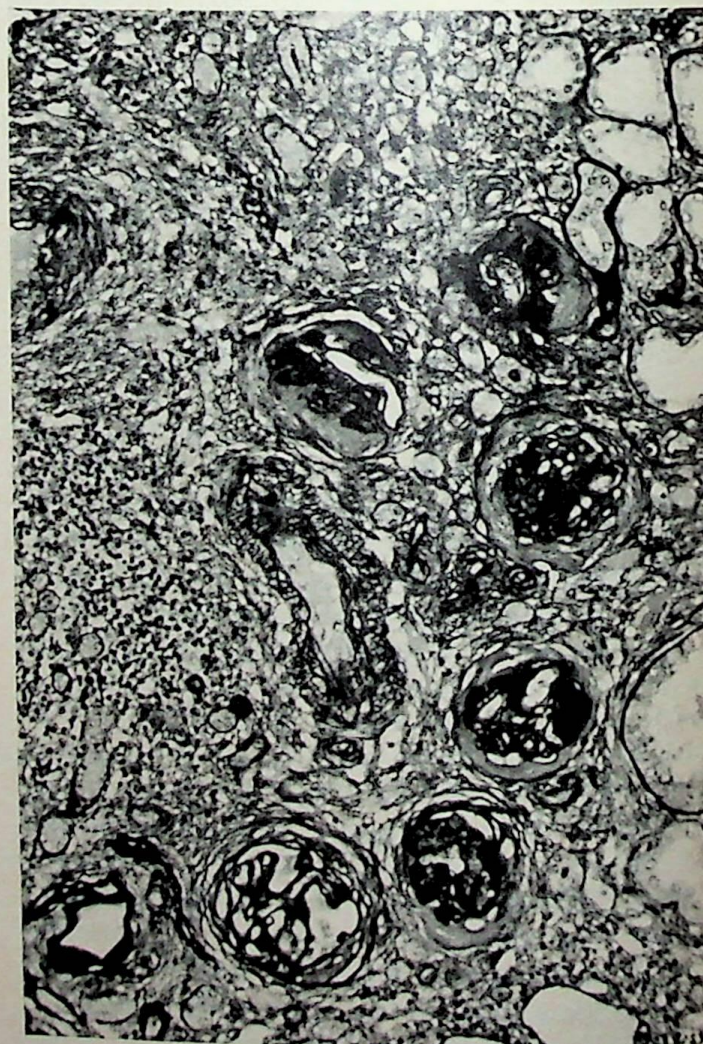
Fig. 4. This section of renal cortex illustrates glomerular hyalinization with mild periglomerular fibrosis and diffuse mononuclear interstitial infiltrate. (Periodic acid-Schiff; ×400.)

Fig. 5. Illustration of tubular dilatation and tortuosity amid other atrophied tubules in this section of renal medulla. (Periodic acid-Schiff; ×400.)

recent case reports have concluded that the disorders are indistinguishable morphologically. Analyses of the mode of genetic transmission have differed. Gardner[4] has suggested that the conditions are separable by their inheritance patterns and age at onset. He believes that juvenile nephronophthisis is an autosomal recessive condition with onset during infancy, childhood, or adolescence; the adult-onset type (cystic disease of the renal medulla) is inherited as an autosomal dominant.

Early reports of medullary cystic disease and nephronophthisis suggested that an embryologic developmental anomaly was the cause. The primary generation of uriniferous tubules eventually lies in the medulla, where the cells normally undergo cystic degeneration. It was hypothesized that these primary tubules do not undergo complete degeneration but persist as degenerating cysts.

Other investigators[9,18] believe that the cysts are a secondary development of a primary tubular process. Sworn and Eisinger[9] observed that cysts were present in the kidney of one girl and not in her younger sibling. This sibling had all the clinical and histologic features of the disease except for medullary cysts. Sworn and Eisinger's observations suggest that cysts may occur or become more prominent with the length of survival.

Pyelonephritis conceivably could be the etiologic agent for the changes; Goldman and associates[20] found clinical evidence of infection in seven patients. There is some histologic resemblance of this disease to pyelonephritis, but most reports have noted the lack of historical or clinical evidence for a urinary tract infection. The bilaterally symmetric kidney damage, which is uniform throughout the tissue, is evidence against infection.

The most attractive pathogenetic theory is that a nephrotoxic substance, possibly the product of an inborn enzymatic defect, leads to early tubular dysfunction and then to progressive renal failure.[16,17] This course is similar to that of toxic nephropathies. Several authors have noted the similarity of this syndrome to Balkan nephropathy, which is thought to be an environmental disease although no toxin has yet been identified.[10,17,21] Patients with cystinosis have the same decreased renal concentrating ability, high filtration fraction, renal osteodystrophy with growth failure, and early death as do patients with familial juvenile nephronophthisis or medullary cystic disease. Signs of proximal tubular failure such as glycosuria and aminoaciduria, which are found in cystinosis, are absent in cystic disease of the medulla.

Differences in the nature or amount of toxin might explain the varying age at onset, rate of progression, and cyst size. Sporadic cases might be related to exposure to an exogenous toxin.[17]

Safouh and co-workers[22] offer support to this theory with experiments in which they fed diphenylamine to rats. Within 5 weeks, the maximal urinary concentrating capacity was decreased significantly. At 2 months, they found early collecting tubule dilatation and saccular formation in the outer medulla which progressed with the duration of the experiment.

Data also showed a decreased papillary urea concentration that could disrupt the countercurrent mechanism enough to create the observed defect in concentrating ability. Safouh and associates[22] suggested that diphenylamine might interfere with the active transport of urea from the collecting duct into the interstitium.

Herdman and associates[16] also believed that the early inability to concentrate urine was related to

altered urea transport secondary to a toxic inborn error of metabolism. Increased thickness of tubular basement membranes, peritubular fibrosis, and a direct toxic effect on tubular epithelium are all possible explanations of a defect in urea transport. Morphologic evidence of excessive fluid transport across the epithelial cyst lining has been found.[15]

Renal transplants have not yet been found to undergo medullary cystic changes in patients with this disorder.[4,14,23,24] This does not rule out as a plausible cause the possibility of a nephrotoxic substance coming either from an exogenous source or produced as the result of an inborn error of metabolism. In patients with cystinosis, the transplanted kidney does not develop the histologic or functional changes of the original disorder.[24,25]

With evidence for at least two modes of inheritance, the similar pathologic findings do not rule out two or more possible etiologies. The histologic picture of end-stage renal disease is similar in a wide variety of disorders even though the primary renal defect may be tubular, glomerular, or interstitial.

Table 3.—**Classification of Reported Cases by Mode of Inheritance and Age at Onset**

Juvenile nephronophthisis 1. Autosomal recessive 2. Childhood onset		Cystic disease of the renal medulla 1. Autosomal dominant 2. Adult onset	
Author	No. of patients	Author	No. of patients
Fanconi et al[8]	8	Goldman et al[20]	14
Smith and Graham*[26]	1	Gardner[4] (family B only)	6
Mongeau and Worthen[17] (cases 4, 5, 6, and 7 only)	7	Wrigley et al[5]	9
Herdman et al[16]	4	Axelsson and Ödlund[6]	4
Sworn and Eisinger[9]	3	Total	33
Case 9-1975*[23]	1		
Friedman and Rattazi[27]	2		
Handa and Tennant[10]	2		
Gibson and Arneil*[28]	8		
Ljungqvist et al[11]	4		
Giselson et al[29]	2		
Spicer et al*[12]	1		
Price and Pratt-Johnson[13]	2		
Pascal*[15]	1		
Habib[7]	22		
Present series	9		
Total	77		

*Indicates single cases for which Gardner[4] suggested a third category, sporadic cases. They are also compatible with recessive inheritance as we have listed them.

Note: Kyle's[30] series of 7 cases and Makker and associates'[31] 15 cases were excluded as atypical. Giangiacomo and associates'[32] series of 10 was excluded from the table due to the disputed mode of inheritance. The cases of Pedreira and associates[3] and Mangos and associates[33] were excluded since they are equally compatible with autosomal recessive or dominant inheritance with incomplete penetrance (10 cases). Twenty-eight patients of Habib's[7] series of 50 patients had no positive family history.

As previously mentioned, analyses of the mode of transmission of this disorder have led to different conclusions. Our own conclusions agree with Gardner's classification[4] by mode of inheritance and age at onset. Using this classification, we have categorized a number of papers on nephronophthisis and medullary cystic disease (Table 3). Reports of atypical or disputed cases were excluded.[30-32] All single cases in a family were categorized as recessive, though we recognize that they are also compatible with Gardner's third category, nonfamilial medullary cystic disease (that is, sporadic disease).[12,15,23,26,28]

We found two reports of patients' relatives who had decreased urinary specific gravity, polyuria and polydipsia, or both, but no other manifestations of renal disease.[3,33] These were excluded from Table 3. The cases seem best explained as heterozygotic manifestations of an autosomal recessive trait. The known affected members of both families were children. They would fit into the recessive, juvenile-onset category. However, we recognize such cases could as easily be called evidence for autosomal dominant inheritance with incomplete penetrance.

A recent publication[32] that refutes Gardner's classification presents a family with childhood onset of cystic disease of the medulla and apparent autosomal dominant transmission. We do not believe that the pedigree analysis of this family is conclusive for autosomal dominant transmission. Parents of the known affected siblings had no renal disease. There is no conclusive clinical or histologic data that suggest patients III-1 and III-7, two siblings of the father, had the same disease as the proband and siblings. Two family members of generations I and II had late adult-onset renal disease. This is clearly different from the juvenile-onset disorder seen in the siblings of generation IV.

Makker and associates[31] have described juvenile-onset, autosomal, dominantly inherited renal disease in a pair of monozygotic twins. The hematuria, heavy proteinuria, and prolonged course of the disease in their patients, considered along with the absence of early onset of anemia, azotemia, hyposthenuria, polyuria, and polydipsia, suggest a different disorder. The diagnosis of juvenile nephronophthisis must be based on a combination of characteristic clinical, laboratory, and morphologic findings.

The ratio of affected to unaffected siblings among those we classified as autosomal recessive was 29:80.

This is not a statistically significant deviation from the expected 1:3 ratio.

The total male to female ratio of all reports, including our own series, was 1.4. However, we do not believe juvenile nephronophthisis is selectively male preponderant or has an X-linked mode of inheritance.[34] It is interesting that if the contribution by three large families is excluded the ratio becomes 0.86.

SUMMARY

We have described the occurrence of juvenile nephronophthisis in six of a total of nine affected children from four families. The disease is characterized by polyuria, polydipsia, decreased urinary specific gravity, anemia, azotemia with progressive renal failure, and death. The changes of renal osteodystrophy are often seen in affected children. Pathologic findings in all forms of the disorder are identical.

The most attractive pathogenetic mechanism proposed suggests the action of a nephrotoxic substance present as the result of an inborn error of metabolism. We believe the evidence for two modes of inheritance suggests two different etiologies. The juvenile-onset, recessive form with the more rapid, progressive renal failure and early death may be due to an inborn enzymatic defect as proposed by other authors. The adult-onset, dominant form usually has a more prolonged course. Its etiology could be a structural defect of protein.

In this series, the siblings had no previous family history of renal disease. The presumed mode of inheritance is autosomal recessive. The age at onset and mode of inheritance are compatible with Gardner's juvenile-onset type of familial medullary cystic disease and Fanconi's original description of juvenile nephronophthisis.

We believe Gardner's classification is the best approach yet to understanding the confusing spectrum of disease encompassed by the names juvenile nephronophthisis and medullary cystic disease of the kidney.

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Concussion

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We have observed the effects of concussion on nonanesthetized rats and humans. We believe the phenomenon in both to be identical. There are four obvious stages to concussion and the recovery therefrom: fourth stage—visceral (respiratory) and somatic immobility; third stage—return of irregular visceral (respiratory) mobility with continuing somatic immobility; second stage—normal visceral mobility with impaired somatic mobility; and first stage—normal somatic mobility with impaired performance. Zero stage is complete normality. Our method of testing detects no lingering or permanent change after a single concussion. This proves only that we must continue with open minds on the question, "Does concussion always leave permanent brain damage?"

Concussion has been recognized throughout history and possibly was recognized by our primate ancestors. It continues today to be, if not the leading cause for admission to our emergency wards, certainly a legitimate contender for that dubious distinction. Of all injuries it behaves in the most consistent manner and certainly in the most spectacular manner. For over 3,000 years it has been the subject of poems, novels, scientific articles, legends, and folklore[1]—with the boundary not always distinct between these groups. Today we know little if anything more about the phenomenon than did our medieval medical forefathers. The word "concussion" never appears in the index of Fulton's *Physiology of the Nervous System*[2] nor in Sherrington's *Integrative Action of the Nervous System*,[3] yet most of their classic preparations could be given a concussive blow and the experiment repeated. Thus, if any readers feel despondent because all of the research has been done on the nervous system, there are some 12 or so new starting points, each of which in turn would doubtlessly open up additional portals of investigation.

Most of our knowledge of concussion comes from observations on the human model, and down through the ages he has been a most obliging model up to a point. He has waged almost continual warfare, and even in current peacetime North America he goes aggressively to and from work in a high-powered vehicle, usually just a little faster than he should. He goes forth to compete at the various rings, and rinks, and fields, and arenas, and for other forms of amusement he attends bars and political rallies. From these sources alone we harvest 1,500 well-documented cases of concussion at our center each year. The combined world neurosurgical experience down through the years must total many, many millions of well-documented concussions. But from all of this we possess few facts.

We know that concussion over the cord results in an instantaneous diminution or loss of function followed by a rapid and complete recovery and that concussion to the head results in an instantaneous diminution or loss of function or consciousness, or both, followed by a rapid and complete recovery. If consciousness is lost, the individual experiences no

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sensation until his sudden, rather surprised awakening; the episode is surrounded by a sphere of amnesia which rapidly shrinks to a finite minimum including about one-tenth of the total as retrograde amnesia. Thus, the boxer never remembers the knockout blow.

We define concussion as a transient disturbance of neuronal function as a result of trauma, with no demonstrable gross or microscopic changes. We know there must be changes—electrical, chemical, polarization, or ultramicrostructural—but as yet we have not been able to identify them.[1,4] It is evident that with concussion, millions of neurons cease to function and then rapidly return to normal function and continue indefinitely. We now approach one of the many unknowns of this phenomenon. Should we believe that each one of these normally functioning neurons retain some lingering or permanent damage, or that some selected neurons retain some lingering or permanent damage, or that none of them retain any residual damage? We all agree that many head injuries do more than concuss; they contuse, or lacerate, or damage cranial nerves or the middle ear. Thus, it is evident that many patients who have concussion suffer permanent intracranial damage. But the question confronting us may be worded in two ways: Does every case of concussion produce lingering or permanent brain damage? Or is it possible to be concussed without suffering lingering or permanent brain damage? The question is not merely academic. Depending on how we answer this question, large sums of money are given or withheld by the courts.

Research begins by asking nature a question, and this question is well and properly asked. But research continues with an orderly series of investigative procedures designed and programmed with controls to arrive at an answer; these procedures are observed, recorded, and interpreted without bias. All this has not been easy with human models. Most of the skills possessed by humans are not readily and accurately measurable and most of the sophisticated tests given humans after concussion were not given to them before concussion. Moreover, many of the concussed individuals given sophisticated tests have conceivable reasons for doing less than their very best on these tests.

Articles in the literature understandably have described small groups without controls. A group of individuals were given a battery of tests because long after their concussions they experienced headache, dizziness, and other symptoms whenever they tried to go back to work.[5] Another investigator would place more emphasis on the compensation factors.[6] Others found some ex-boxers and ex-soccer players whose behavior was considered less than acceptable to polite society and they were found to have abnormal electroencephalograms.[7] Another investigator suggests that similar individuals could be found who have never been concussed.[8]

These articles appear in reputable journals, and quite properly so. They are quoted, as they quite properly should be. But as each article is quoted the impressions and conclusions of the authors become encrusted with a layer of authority. After the passage of sufficient time and sufficient number of quotes, the encrustations of the barnacles of authority become so thick that nobody bothers to scrape them off and look at the shape of the original hull, which in most instances is best described as anecdotal. Most current authorities indicate a belief that concussion always leaves some permanent brain damage,[2,5,7-13] but a few challenge this.[6,14,15]

Every neurosurgeon in practice for any length of time could describe patients who possess readily measurable skills—typists, musicians, or mathematicians—and who have been concussed fortuitously at their own responsibility and hence have no interest other than to continue doing their very best. Some or all of these individuals, when asked later, will insist that they can detect no difference in their performance, memory, or ability to learn. Again, this is anecdotal reporting. Although most scientists tend to scorn the professional athlete and his much concussed cerebrum, nevertheless these individuals possess remarkable physical skills and very often considerable mental skills. Not only are they desirous of doing their best after any injury but they wish to do their best as soon as possible. In the case of a boxer, he must respond within 10 seconds or the show is over. Sporting annals contain numerous incidents of boxers who have come from the canvas and won the fight or football quarterbacks who have been concussed and gone back and played and called a winning game. Again, this is anecdotal reporting.

Willing as man has been to participate daily in situations in which concussion is a real possibility, he has been spectacularly unwilling to participate in any controlled experiment in which concussion is a certainty. When we turn to the animal laboratories, we have been constantly thwarted by the insistence that the animal must be anesthetized if he is to be concussed. There is one article in the literature that leaves doubt concerning this, but I have corresponded with the author and find that the animals were anes-

thetized before their concussion,[16] thus leaving us the dubious task of untangling the uncertain sum of two nervous system depressants.

We were turned down in our request to concuss nonanesthetized animals for 20 years, even though we argued that from the human model we know that concussion produces instantaneous loss of consciousness. Recently, a very enlightened University Animal Experimentation Committee granted us permission to concuss nonanesthetized rats. At the onset we were delighted although not surprised to see that these rats behaved just as did their human counterparts, showing no evidence of suffering and no evidence of recollection. At no time did they cry out as they were struck nor have they ever cringed from going back to the concussing hammer, other than their customary struggle against any form of restraint. This is in considerable contradistinction to the behavior of similar rats in long-approved experiments where they cry out at the needle administering the anesthetic and cringe and cry out even more the second time because they remember the first episode.

For our experiments we use the Sprague-Dawley strain of white rats, keeping two of each group as feeding controls. Each rat is introduced to and trained in progressively more complex mazes. Our maze provides seven grades of complexity with two patterns in each grade for a total of 14 patterns.

A diary is kept for each rat, recording his optimal performance, his speed of learning, and his memory for each maze. After each rat has learned one-half of the mazes in each category of complexity and after there has been sufficient time to evaluate the rate of his memory decay, the rat is concussed and the entire procedure continues. His postconcussion performance is compared with his preconcussion record as well as with the continuing performance of the nonconcussed contemporary controls to encompass the aging factor.

Movies both of boxers and of rats point up several features. There is a comparative lack of calibration of the otherwise scientifically designed ultraprecision concussing mechanism for the rats. However, the rats are awake and, although their bodies are restrained under the hammer, their heads are moving constantly. If you have ever boxed, you will remember that the third thing you learn is that if you cannot block or duck a punch you should get your head turning away from it. In the movies of boxers there is often a seemingly impossible barrage of blows to the head, which are absorbed without knocking the boxer off his feet in some instances. Sometimes an uneducated sports writer will insist that the opponent does not have a knockout punch. But when a boxer is caught with his head stationary or—even worse—turning toward the oncoming blow (as with a left hook followed by a right cross), the boxer goes down so quickly from a seemingly innocuous blow that the same uneducated sports writer may shout that he "took a dive." Every boxer knows that an axial blow to the head is the least damaging and that the most devastating blow is one that sets the head rotating on its long axis.[17] The resultant swirling movement of the brain was demonstrated beautifully years ago in the lucite calvarium experiments of Pudenz and Sheldon.[18]

It is more difficult to see this phenomenon in the rat but the principle is still there. They are always struck an axial blow but if their head is moving toward the hammer, they are much more severely concussed than if the head is stationary or moving away from the hammer, in which case they are sometimes barely stunned. Thus, the severity of concussion is not the simple product of a single factor, the force of the blow. It is a complex multiple of several factors including the force of the blow, the direction of the blow, the direction the head is moving when the blow is struck, the speed the head is moving in that direction, the weight of the head, and hence the inertia and even the texture of the surface administering the blow. For instance, the force of a fairly slowly moving but heavy ball peen hammer may produce a small depressed fracture without any concussion. The same force administered by a lighter but higher-velocity and softer-surfaced baseball may severely concuss.

If the severity of concussion cannot be measured by the force of the blow, how is it measured? It is the concussion that we are evaluating and we measure this by the total time of somatic immobility. This is the next item to be observed in the movies. It is possibly better seen in rats than in boxers. It is brief in all instances. We know that it is accompanied by a marked suppression of visceral activity but this cannot be demonstrated in movies.

The next feature is that there are four stages to concussion and recovery from it, each following rapidly on the other. Stage four is that of visceral (respiratory) arrest along with somatic immobility. This is followed rapidly by stage three, which is a continuation of somatic immobility with a return of respiratory movements which are shallow and irregular. This is again followed rapidly by stage two—a return of normal respiratory movements and of

somatic mobility which is inadequate, ineffective, and sometimes inappropriate. It is easily seen in the boxers in their ineffective efforts to get up from the canvas or, if they are back on their feet, by their flat-footed, rubber-kneed gait and sometimes by their inability to hold their arms up to defend themselves. The first stage follows immediately and is one of normal mobility. There is normal posture, gait, speed, and attitude, and yet if the rat is put immediately into the maze his performance is slow and he makes some errors. This first stage, normal mobility but impaired performance, lasts longer than the preceding stages but is rapidly followed in turn by stage zero, which is that of complete recovery. The rat's performance in the maze is normal and it remains normal thereafter.

It is difficult to detect stages two and one in pictures of boxers. The devastating effect of the blow that catches the head moving toward the fist and sets it spinning is well seen in the slow motion films of fights. In many instances, in both boxers and rats, concussion does not take the subject down as low as stage four and he may only descend to stage three or stage two.

One feature we cannot explain but see frequently with the rats is their unpredictable refusal to leave the starting box after the gate is lifted. This occurs without reference to whether they have been concussed or not. They may decide to stay in the starting box in the middle of several successful runs. We accept it as one of the idiosyncrasies of the rats' personalities. One of our residents suggested that the old lags in the cages at night tell the younger ones that they "shouldn't get too good at it or they'll whack you one on the head." We learned very early to time the run from the moment the rat has decided that he is going to run the maze and not from the moment the gate is lifted. The rat at times may come out of his starting box and look around and go back in and it is quite evident from his attitude that he has not decided he is going to run the maze at that point. He may simply be exerting his independence.

Figure 1 shows the pattern of an experienced rat confronted with a new maze. The vertical axis above is the time and the horizontal axis is the number of runs. The curve levels out at his optimum time, which in this instance is 6 to 7 seconds, and he will continue to perform at that speed indefinitely. The vertical line below indicates the number of mistakes, which eventually becomes 0. The rat will continue this performance indefinitely—0 mistakes and 6 to 7 seconds running time for that maze. Rats vary in
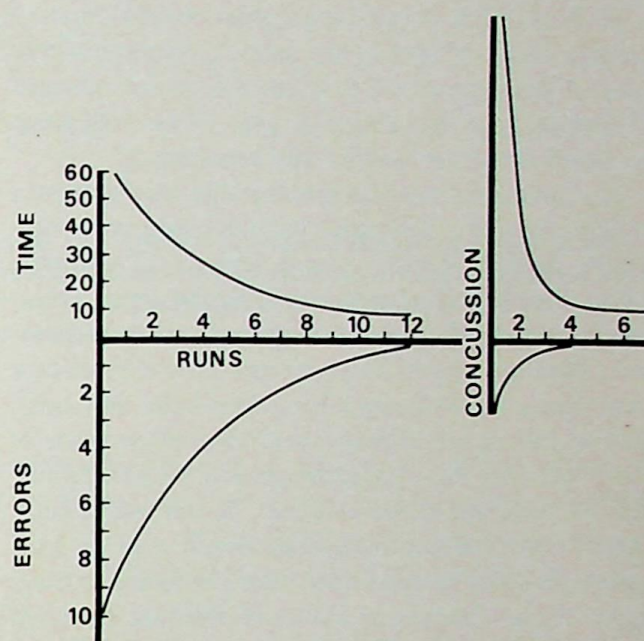
Fig. 1. Graph for rat running moderately difficult maze showing that after 12 runs he reaches optimum of 6 to 7 seconds with no mistakes, having started at about 60 seconds with 10 mistakes. The break in continuity indicates time occupied by concussing blow and recovery back to stage one, at which point he is put in maze. He takes long time to complete first run yet makes only three errors. By fourth run, he is making no errors but is still few seconds slower than his preconcussing optimum. By sixth run he has returned to his optimum performance.

their intelligence; there are slow learners and fast learners, and show-offs, and sulky ones. They are much like humans. But each rat will have a similar overall pattern, although the slow learners may start with a longer time and more mistakes and, with a more difficult maze, the curve will start higher. But the curve is similar and in all instances levels out at no mistakes and at the optimal time for that given rat in that given maze. Next we see the effect of a concussing blow; in this instance, stages four, three, and two have passed in the blank interval and the rat is put in the maze at stage one. This rat has normal mobility but he takes a long time and makes a few mistakes. The increase in time is far greater than the corresponding increase in the number of mistakes..

During the course of our experiments many rats were concussed less than enough to reach stage four. Their performance returns to normal much more quickly but only the rats whose concussion depressed them to stage four are used for these evaluations. The rat that is merely stunned (stage two or even stage one) takes a much shorter time in stage one, but in all instances the performance is impaired for a measurable time—anywhere from less than a minute up

to an hour. The performance then remains normal through the rest of his life span. The normal life span of this type of rat in a laboratory environment is supposed to be about 1 year. Our rats have averaged about 18 months' life expectancy.

We have now run 20 rats through this sequence of learning half of the mazes in each category of complexity, then being concussed, and then continuing with testing and observations. Only those rats whose concussions took them to stage four are being counted. Twenty others have served as contemporary controls without concussion. We have not been able to detect any difference in the performance of these rats after this single concussion. We recognize that the next question has to be: "Is our testing sufficiently fine to detect residual damage?" and we must answer that we do not know. We can resort to sheer logic. If one concussion leaves no residual, then two concussions leave no residual—or any given number will leave no residual. This is ignoring for the moment the factor of elapsed time between concussions. We can also argue that if the effects of concussion are cumulative, then, recognizable or not, there is some residual from a single concussion. Thus, multiple concussions would magnify the observations and the validity of our experiements. We propose to do this for the next series. Six months ago we concussed one rat five times at approximately 2-day intervals and one rate five times at approximately 2-minute intervals. To date, we can detect no difference in their subsequent performance, learning, or memory. But this is not a sufficient number to be significant.

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Subject Review

Middle Ear Effusions
Current Concepts

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Current concepts of middle ear effusions in childhood including a discussion of etiology, diagnosis, and treatment are presented. We emphasize recent studies on the histochemical makeup of the middle ear, as well as the enzymatic and immunologic defense systems of that space. The mucociliary transport system is explained and recent literature is reviewed.

There has been a tremendous output of papers on the topic of middle ear effusions, such that it is difficult to keep up with the advancing knowledge of this field and correlate it with classic concepts of the past. We present an overview of middle ear effusions, including a review of some of the important recent literature.

Middle ear effusion has many names, including serous otitis media, secretory otitis media, glue ear, mucoid ear, middle ear catarrh, tubotympanitis, allergic otitis media, and others. We define it as sterile fluid in the middle ear, often resulting in decreased motility of the tympanic membrane with varying degrees of conductive hearing loss. When the middle ear becomes infected, the term acute suppurative otitis media is appropriate. The remarks in this paper, however, will be confined to nonsuppurative otitis media.

HISTORICAL PERSPECTIVE

Politzer[1] first used the term otitis media catarrhalis in the late 1800's and described the basic principles of ventilation and drainage that have remained tenets of treatment. The increased use of antibiotics to treat purulent otitis media and the aviation-related study of barotrauma stimulated much interest in serous otitis media in the 1940's. In the mid-1950's, the concept of inserting a polyethylene tube through the tympanic membrane to improve the middle ear ventilation was introduced.

Recent studies have dealt with the cytologic and histochemical makeup of the middle ear system. Recent work has also dealt with the chemical, enzymatic, and immunologic defense systems of the middle ear, with emphasis on the mucociliary transport system of the middle ear and eustachian tube. Discussions of the pathogenesis of middle ear effusion often center on mechanisms of eustachian tube dysfunction. Diagnosis of middle ear effusion has been improved through the use of the pneumatic otoscope and tympanometry.

INCIDENCE

There is a significant incidence of middle ear effusion in children, which seems to be increased[2] among the poor and the Eskimo and American Indian populations and in cold environments. Sadé[3] has estimated that 5% of Israeli schoolchildren have middle ear effusion. Bluestone and Shurin[4] showed that 20% of children in their study at 5 years of age had middle ear effusion; this was reduced to 3% at 10 years of age. This age-related incidence is further seen in Oppenheimer's[5] report of 922

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cases of middle ear effusion. He notes that 20% of the patients were under 2 years of age, 55% were between 2 and 5 years of age, 15% were 5 to 8 years of age, 7% were 8 to 12 years of age, and 3% were over 12 years of age.

CLASSIFICATION OF THE EFFUSION

Middle ear effusion is classified as serous, mucoid, or bloody. In classic acute serous otitis media, often following recent upper respiratory infection or barotrauma, the middle ear contains a yellow or clear fluid of low viscosity which is a transudate from the serum. Mucoid effusions, often termed glue ear, consist of cloudy, thick fluid—the result of active secretion by glandular epithelium in the middle ear. Bloody effusions are associated with trauma, blood dyscrasias, or barotrauma. The typical appearance of the tympanic membrane results in the term blue eardrum.[6]

ETIOLOGIC CONSIDERATIONS OF MIDDLE EAR EFFUSION

Many causes for middle ear effusion have been proposed.[7] Some of these etiologic factors are outlined in Table 1 and discussed below.

Eustachian Tube Dysfunction.—One of the main underlying themes used to explain the pathogenesis of middle ear effusion is dysfunction of the eustachian tube. Bluestone and associates[4,8-10] have written extensively on this subject. Eustachian tube dysfunction is a purposefully vague term describing inadequate ventilation of the middle ear space. Resulting negative pressure is the main factor in fluid formation in the middle ear. It is possible that a large majority of children with recurrent serous otitis media (without a specific demonstrable cause) have a growth-related inadequate action of the tensor veli palatini (the main opener of the tube). Thus at about 12 years of age many children will develop better muscle action and their recurrent middle ear effusions cease to be a problem. It is useful to point this out to parents.

Table 1.—**Outline of Etiologic Factors in Middle Ear Effusion**

- Eustachian tube dysfunction
- Barotrauma (aerotitis)
- Cleft palate
- Adenoidal hypertrophy
- Allergy
- Infection, inflammation, and the use of antibiotics
- Miscellaneous factors
    - Endocrine disorders
    - Oncologic disorders
    - Radiation effects
    - Surgical trauma

Barotrauma (Aerotitis).—This process is most commonly seen as a result of air travel but can occur in any situation involving rapid, significant atmospheric changes. When pressure in the nasopharynx exceeds the middle ear pressure, the eustachian tube opens to equalize the pressures. This opening is caused by the contraction of the levator and tensor veli palatini muscles. When this fails to happen efficiently (for example, when the change in pressure is rapid), the tympanic membrane retracts and pain occurs. Failure of equalization of middle ear pressures can cause disruption of middle ear capillaries and transudation of serum into the middle ear. Air in the middle ear will be absorbed, causing an increased negative middle ear pressure. This is called barotrauma or aerotitis.[11] Its incidence has increased because of greater interest in air travel and deep-sea diving. Many patients can prevent this by swallowing repeatedly. People prone to aerotitis should not fly when they have an upper respiratory tract infection.

Cleft Palate.—An increased incidence of middle ear effusion and purulent otitis media occurs in children with cleft palate. This is due to dysfunction of the muscles controlling the eustachian tube. Inability to move foreign particles from the nasopharynx to the eustachian tube is demonstrated by x-ray studies and air-flow studies indicating eustachian tube dysfunction.[9] There is difficulty equilibrating pressure changes. The hearing loss in these children is usually bilateral; it is conductive, of course, and is seen in more than 50% of patients studied.[12] Bluestone and associates[9] report that 50% of patients were free of middle ear effusion 6 to 12 months after the repair of their cleft palate

Adenoidal Hypertrophy.—Extrinsic obstruction to the opening of the eustachian tube by enlarged adenoids has long been cited as a factor in some children with middle ear effusion. Persistent nasal obstruction, mouth breathing, and an adenoidal facies are suggestive of adenoidal hypertrophy. Lateral roentgenograms of the nasopharynx documenting adenoidal hypertrophy are useful in evaluating a child with persistent middle ear effusion because mirror inspection of the nasopharynx in children is often difficult. Rather than imagining the adenoid pad actually obstructing the opening of the eustachian tube and the nasopharynx, it is a more attractive hypothesis to suppose that large adenoids can obstruct the lymphatics of the eustachian tube, producing middle ear effusion subsequently. Chronic adenoid-

itis may serve as a source of eustachian tube infection with resultant middle ear effusion and infection. Fraser[13] questions this concept. He states that there is no evidence for enlarged adenoids or chronic adenoidal infection in many patients with middle ear effusion. Adenoidectomy for treatment of middle ear effusion is still controversial. At this institution, we avoid the ritual removal of adenoids when doing myringotomies for middle ear effusion. Adenoidectomy is performed only when separate and clear criteria for adenoidectomy are documented.

Allergy.—The role of allergy in middle ear effusion also remains controversial. Jordan,[14] in 1949, stated that allergy factors were the cause of 74% of the middle ear effusions in his series of 123 patients. Derlacki[15] thought that allergy to house dust or food was the prime factor in the majority of his patients with chronic middle ear disease. Draper[16] studied middle ear effusion in 560 children and found the incidence of allergic manifestations was twice that of controls. Bierman and associates[17] noted a 22.6% incidence of middle ear effusion in 1,222 children with allergies. Dees and Lefkowitz[18] found allergic manifestations in 85% of children with recurrent middle ear effusions seen in their allergy clinic; 80% improved with allergy treatment, including desensitization programs. Friedman[19] also thinks that allergy is the main cause for recurrent middle ear effusion in children. Rapp and Fahey[20] believe that allergy treatment desensitization, in particular, is of definite value in some patients with middle ear effusion. However, studies of Mogi and associates[21,22] indicate that atopic allergy may not be a significant factor in the formation of middle ear effusions. They found IgE in middle ear effusion and indicated that it is derived from the serum and is not a product of local mucosal secretions. Clemis[23] and others have taken a more moderate view by saying that allergy is but one of many etiologic factors that must be evaluated in patients who have persistent middle ear effusion.

Infection, Inflammation, and Antibiotics.—Nasal, paranasal, or nasopharyngeal suppuration has been implicated in the development of middle ear effusion. Nasopharyngeal secretions aspirated into the middle ear may be a factor. Brookler[24] has indicated that the bacteria associated with nasopharyngitis may produce proteolytic enzymes that can destroy the surfactant material of the eustachian tube and contribute to eustachian tube dysfunction. Bernstein[25] has isolated four separate mediators of inflammation—chemotactic factor(s), macrophage inhibition factor(s), activated complement, and prostaglandins—in middle ear effusions. These factors may contribute to persistent middle ear inflammation with resultant persistent outpouring of fluid by the irritated mucosa of the middle ear.

There is no evidence for a direct viral infection as a cause of middle ear effusion.[26] Klein and Teele[27] reported the isolation of viruses (mostly respiratory syncytial virus) in only 4.4% of 633 patients with middle ear effusion. Incomplete antibiotic therapy for middle ear infection may be a contributing factor. Friedman[19] studied over 400 children who had myringotomy as part of their evaluation for middle ear effusion. All received what he felt was an unsatisfactory course of antibiotics for their middle ear disorder. Such treatment may allow the development of a chronic low-grade infection that may stimulate the middle ear mucosa to produce a chronic outpouring of fluid.[28] Raikundalia[29] thinks that the early use of antibiotics to treat middle ear infection contributes to the development of middle ear effusion. Indicating that there may be bacteriologic contamination of middle ear effusions, Liu and associates[30] reported finding bacteria in smears of chronic middle ear effusion of 80% of 172 patients; 49% had positive bacterial cultures. It is evident that the precise role of inflammation, infection, and antibiotic therapy in the pathogenesis of middle ear effusion remains unclear at the moment.

Miscellaneous Factors.—Middle ear effusion may be associated with such conditions as hypothyroidism, adrenocortical insufficiency, hypogammaglobulinemia, nasopharyngeal tumors, leukemia, and lymphoma. Damage to the eustachian tube from the effects of radiation and from trauma during adenoidectomy may produce fluid within the middle ear. The basic mechanism for these factors seems to be eustachian tube dysfunction.

THE MUCOCILIARY TRANSPORT SYSTEM

Recent investigations have centered on the mucociliary transport system[31] as the first line of defense for the middle ear in preventing physiologic disruption. This system contains ciliated cells, secretory cells, and a mucous blanket. The middle mucosa contains an epithelium and subepithelial connective tissue. Goblet cells and mucous glands provide a mucous blanket, which, along with ciliated cells, aids in the removal of foreign particles from the middle ear. This mucociliary action was shown by Sadé,[32,33] who observed the evacuation of particles from the middle ear to the nasopharynx within minutes of their introduction into the middle ear. Part of this

transport system is the movement of large molecules from the mucosal surface toward connective tissue layers for phagocytosis by histiocytes or for transport to capillaries or lymphatics. After their study of premature and full-term newborns, Bak-Pederson and Tos[34] concluded that mucous glands do not form part of the normal initial component of the mucosa of the middle ear. A limited number of these glands will be found in older children who have little or no history of middle ear effusions. It is generally believed that a few minor upper respiratory infections can lead to the formation of some mucous glands in the middle ear mucosa, which can produce a small amount of fluid without clinical symptomatology. Frequent upper respiratory infections may produce a significantly higher density of mucous glands in some individuals, resulting in more fluid production and clinical evidence of middle ear effusion. Tos[35] has reported on his study of 5,000 biopsies taken from 144 temporal bones of individuals who had varying histories of acute and chronic middle ear disorders. He concluded that normal ears contain a low density of goblet cells, no mucous glands, and slight mucus production. Acute middle ear effusions are associated with higher gland density and more mucus production. Ears in which there is chronic serous otitis media are characterized by a high goblet cell and mucous gland density with even more mucus production. In severe disease, such as in glue ear, there may be a high density of inactive and degenerated glands. Variations of this pattern are also described.

ANALYSIS OF MIDDLE EAR FLUID

Detailed biochemical and immunologic analyses of middle ear effusions have been done to determine whether this fluid is an exudate secreted by the middle ear mucosa, a transudate derived from the serum, or both. Reports of the presence of greater levels of IgA[36] and acid phosphatase[37] in this fluid than are found in serum are thought to reflect some local mucosal production. Experimental support is seen by the work of Hussl and Lim,[38] who noted the presence of IgA- and IgG-producing plasma cells in the middle ear mucosa of monkeys in which middle ear effusions were induced. Liu and associates[39] noted higher levels of IgA and IgG in human middle ear effusions than in serum, thus indicating some local mucosal production. However, Mogi and associates[21] concluded that much of the middle ear fluid was due to transudation. Yet they also found some locally produced secretory IgA in effusion fluid which was similar to secretory IgA of other mucosal derivation.[22] More evidence for the concept of some local production was given by Bernstein and associates,[40] who noted the presence of five specific types of protein found in middle ear effusions and not in serum. Tomasi[41] describes a process of local antibody synthesis within the middle ear which is a type of cell-mediated immunity occurring independently of systemic immunity.

DIAGNOSIS OF MIDDLE EAR EFFUSION

Middle ear effusion may present as hearing loss, earache, or both.[42] The hearing loss is bilateral and conductive and is usually associated with a 10- to 40-decibel loss, as measured by pure tone audiometry. Simple hearing tests, such as screening audiometry and the Rinne or Weber test in the young child, may easily miss this condition.

The diagnosis may be made on physical examination on the basis of the appearance of the tympanic membrane (using a standard otoscope),[43] on an estimation of tympanic membrane motility (as seen with the pneumatic otoscope), and on an evaluation of tympanic membrane compliance (as demonstrated by impedance audiometry).

The classic appearance of the tympanic membrane in middle ear effusion is not sufficiently reliable to permit making the correct diagnosis consistently. The light reflex on the tympanic membrane may be diffuse or absent. The membrane may be yellow or gray and may have a retracted or distended appearance. The appearance of the eardrum may also be normal. Thus, in young children who cannot describe symptoms of fullness and so forth, the diagnosis may be overlooked. Poor school progress, speech retardation, and similar problems may be the first manifestations of this capricious entity.

Impedance audiometry has been advocated recently[44,45] to diagnose middle ear effusion without myringotomy. A tone generator and microphone are connected to the external auditory meatus. The entire system is called the electroacoustic impedance bridge and it is used to distinguish conductive hearing loss due to middle ear effusion or ossicular disease. Sound waves are directed at the tympanic membrane and the amount of sound that is reflected from the tympanic membrane is measured. A freely mobile membrane will absorb more sound than one whose movement is limited because of fluid behind it. By changing the pressure within the external auditory canal, tympanic membrane compliance can be measured. Graphs, called middle ear tympanograms, can then be developed which relate membrane compliance to middle ear pressure. Eleven specific

types of tympanograms have now been developed.[46] Bluestone and associates[47] reported a high accuracy rate in diagnosing middle ear effusion, as confirmed by myringotomies. They have advocated the use of the tympanograms as an aid in three basic areas: (1) improving the diagnosis of middle ear effusion when routine methods are unsatisfactory, (2) objectively determining the middle ear pressure, and (3) screening for middle ear disease accurately. The tympanogram is useful for detecting high negative middle ear pressure in patients who do not have middle ear effusions. This may indicate significant eustachian tube obstruction, with the potential for the development of recurrent middle ear effusions.

TREATMENT OF MIDDLE EAR EFFUSION

The treatment of middle ear effusion is controversial. The natural history of acute serous otitis media after an upper respiratory tract infection is such that, despite a high immediate recurrence rate, most cases will eventually resolve without sequelae. Unfortunately, there is a small, unpredictable minority of patients who develop significant complications associated with persistent middle ear effusions.[48-50] The conductive hearing loss that can occur may lead to learning difficulties in the early school years, with lasting effects. Reed and associates[51] showed that significant hearing loss developed in Eskimo children who had severe otitis media. A 10-year study by Kaplan and associates[52] pointed out the resultant verbal and academic disabilities developed by these Eskimo children. Holm and Kunze[53] also reported on the deleterious effects of chronic middle ear effusions on language and speech development in children. Cholesteatoma and the need for tympanic membrane surgery in early adult life have also been reported to be complications of persistent middle ear effusion, or glue ear.

Standard medical treatment has included the use of combinations of various antihistamines and pseudoephedrine. Pseudoephedrine may aid in the removal of middle ear fluid, and antihistamines may be helpful if allergy is part of the underlying mechanism. Miller[54] has indicated that the use of this combination (pseudoephedrine hydrochloride and carbinoxamine maleate) may be useful in some patients with middle ear effusion. At this point, however, it must be stated that there is little evidence that pseudoephedrine, antihistamines, or mucolytic agents[55] aid significantly in the evacuation of middle ear fluid. If concomitant allergic manifestations exist, they should be managed; reports of the efficacy of hyposensitization have been referred to previously.[18] Although the studies of Perrin and associates[56] using sulfisoxazole for recurrent otitis media in children less than 6 years of age may indicate benefit of antibiotic prophylaxis for purulent otitis media, there is no present indication that this is of value for preventing recurrent middle ear effusions. Because eustachian tube dysfunction may be a major factor in the acquisition of middle ear disease, the use of eustachian tube exercises (such as gum chewing, balloon blowing, or the Valsalva maneuver) may be of benefit. Shea[57] has advocated the use of autoinflation therapy for children with middle ear effusion to produce a positive middle ear pressure and improve ventilation.

Surgical treatment includes tonsillectomy, adenoidectomy, and myringotomy with or without the insertion of ventilation tubes. Tonsillectomy has not been shown to be of benefit in preventing persistent middle ear effusion. Although adenoidectomy is a common procedure in most medical centers for some patients with middle ear effusion, the benefits of its use have not been documented by appropriate studies. McKee[58] believes that the incidence of otitis media after adenoidectomy is decreased; Mawson and associates[59] do not agree.

Ventilating tubes have been advocated for middle ear effusion since their introduction by Armstrong[60] in the mid-1950's. As noted, the principle of ventilation and drainage goes back to the teaching of Politzer. Myringotomy alone, according to Archard,[61] is not an effective method of treatment. The benefit of inserting a ventilating tube through an anterior myringotomy incision in the eardrum of patients with recurrent effusion remains controversial.[61] There is an immediate improvement in hearing[62] and the eustachian tube and middle ear ventilation is improved. Whether this allows the altered mucosa of the middle ear to heal is not known. Buckingham and Ferrer[63] emphasized the reversibility in some patients with glue ear who use these tubes. Oppenheimer[5] believes that myringotomy plus insertion of the collar-button type of ventilating tube has the

Table 2.—**Complications Associated With Ventilating Tubes**

Usual operative risks with general anesthesia
Development of purulent otitis media
Formation of a thin membrane at the site of the tube insertion
Persistent tympanic membrane perforation after the tube is removed
Cholesteatoma formation
Tympanosclerosis
Foreign body reaction that may result in earlier removal of the tube
Further hearing loss due to the actual surgery

best chance of keeping the middle ear fluid-free until an improved eustachian tube mechanism can restore normal middle ear function. It is estimated[64] that in 35% of patients a second tube will be necessary and in 11% of patients a third tube will be needed. A report by Kilby and associates[65] seriously questions the value of ventilating tubes, and thus, further studies are needed to resolve these conflicting opinions.

An outline of complications[66,67] associated with ventilation tubes is given in Table 2. In general, insertion of a ventilation tube is advocated for the following reasons: (1) significant hearing loss due to persistent middle ear effusion; (2) tympanic membrane retraction secondary to middle ear effusion; (3) prevention of recurrent middle ear effusion; and (4) correction of significantly increased negative middle ear pressure with hearing loss. In this institution, we first wait watchfully, with or without prescribing a decongestant-antibiotic agent or agents, for middle ear fluid that is recent in onset and nonhandicapping. We use myringotomy and ventilation tubes in those patients in whom the fluid persists and handicapping deafness occurs. As stated, tonsillectomy or adenoidectomy, or both, is only done if there are other specific indications.

COMMENT

Many concerns remain unanswered at the present time regarding middle ear effusion in children. Further analyses of the nature of the fluid present in serous and mucoid effusions are needed to determine the precise role of transudation and exudation in the formation of this fluid. Eustachian tube dysfunction seems to be the main underlying problem in most effusions. The significance of allergy and infection is variable in individual patients and needs further clarification.

Recent studies indicate that the middle ear system has a complicated immunologic defense mechanism of its own, and greater understanding of this mechanism may lead to better methods of prevention and treatment. Impedance audiometry has improved the diagnostic accuracy of middle ear disease, including middle ear effusion. But, as emphasized by Mortimer,[68] the real treatment of serous otitis has not been clarified; and as noted by Stickler and Brownlee,[69] there is a need for further scientific studies with adequate controls to determine which treatment modalities actually are beneficial and under what circumstances positive results can be expected. Currently, the mainstay of treatment remains combinations of antihistamines and pseudoephedrine for patients with acute disease, and myringotomy and insertion of ventilation tubes reserved for those with resistant disease.

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Case Reports

Primary Intraorbital Meningioma With Intraocular Extension

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Intraocular invasion of a meningioma primary in the sheath of the intraorbital portion of the optic nerve was noted in a 54-year-old woman with a 16-year history of visual loss. Seventeen additional cases of intraglobal extension of intraorbital meningioma were found in the literature. The clinical features and histopathologic findings of the total cases are compared and reviewed. We suggest that the mode of penetration is along the course of the posterior ciliary vessels as they penetrate the sclera.

The concept that a meningioma may originate from tissues within the orbital cavity as a primary neoplasm, separate from its usual intracranial position, an idea once viewed with skepticism, has now been amply confirmed by several published series of such tumors.[1-3] Most of these tumors arise within the sheath of the optic nerve from meningocytes that cluster at the tip of arachnoid villi. Rarely, a well-circumscribed intraorbital meningioma will be encountered that is not attached to or a part of the sheath of the optic nerve. These neoplasms may have their origin from ectopic rests of arachnoid cells along some of the nerves in the reticular tissue of the orbital space. Many authors have noted the tendency of meningiomas arising within the sheath of the optic nerve to proliferate and extend in an unpredictable fashion—either intracranially along the optic nerve sheath, to invade the optic nerve proper, or to disrupt the covering dura and grow into the orbital space, or to push anteriorly into the eye. The last is the least common route of extension.

Only a few cases of intraocular extension documented by photographs have been reported in the literature.[4-10] Other examples of intraocular extension will be found in the publication of Karp and associates.[3] The case we wish to report, therefore, is not unique, but we wish to add details of this case to the limited literature on the subject and compare it to others that have been reported.

REPORT OF CASE

A 54-year-old white woman was first seen at the Mayo Clinic in April 1960 because of gradual loss of vision in the right eye of 10 months' duration. The pertinent examinations and ocular findings were: visual acuity of 20/100 in the affected eye with only a residual small central island of vision (Fig. 1), chronic papilledema of the right optic disk, sluggish reaction of the right pupil to stimulation by direct light, negative pneumoencephalogram, and negative roentgenograms of the head and sinuses. On exophthalmometry, the right eye was 1.5 mm more prominent than the left eye, but this difference was considered too small and equivocal to permit a definite diagnosis of proptosis. A diagnosis of indeterminate lesion of the prechiasmal portion of the optic nerve was made. It was decided not to perform an exploratory craniotomy and the patient returned to the care of her local physicians.

Sixteen years passed before this patient was again examined, in April 1976. She related that in 1972 a lateral orbitotomy had been performed elsewhere because of progressive proptosis of the right eye of 4 years' duration. The right

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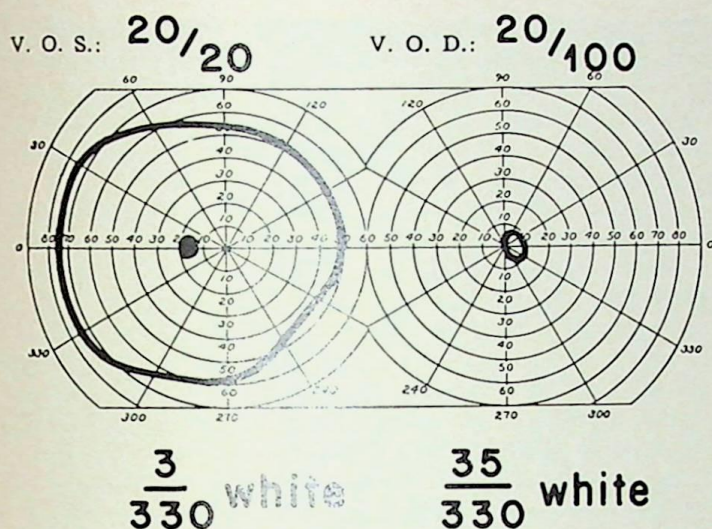
Fig. 1. Perimetric fields on initial visit. Only small central island of vision remains in right eye to largest test target.

Fig. 2. Proptosis and displacement of blind right eye at time of return visit, April 1972. Note chemosis of conjunctiva and edema of right eyelids.

eye had been without sight for some years before this surgery. The tissue removed at the time of orbitotomy was diagnosed as hypertrophied ectopic lacrimal gland. Her concern on the second visit to the Mayo Clinic was the unsightly appearance and continued proptosis of the blind right eye. The eye was proptosed 10 mm and was displaced laterally and inferiorly (Fig. 2). Marked boggy edema of the right eyelids, complete ophthalmoplegia, and total corneal anesthesia also were present. The right pupil was dilated and unresponsive to light stimuli. On ophthalmoscopy, multiple folds of the posterior wall of the eye secondary to increased orbital pressure were noted and the optic disk was pale. The retinal veins in the area of the optic disk were dilated and tortuous. A firm mass was palpable in the superior nasal quadrant of the orbit. Roentgenograms of the head (standard projection) revealed that the right orbit was larger than the left one and that a slightly calcified mass was present in the posterior portion of the right orbit. No bony destruction was observed. Computerized trans-axial tomography confirmed the presence of a retrobulbar mass on the right side; there was no evidence of extension into the adjacent sinuses or the intracranial vault (Fig. 3). The left eye was normal.

The sightless, anesthetic right eye was enucleated by incising the extraocular muscles at their insertions and severing the optic nerve at its junction with the posterior pole of the eye. A grayish, poorly circumscribed tumor
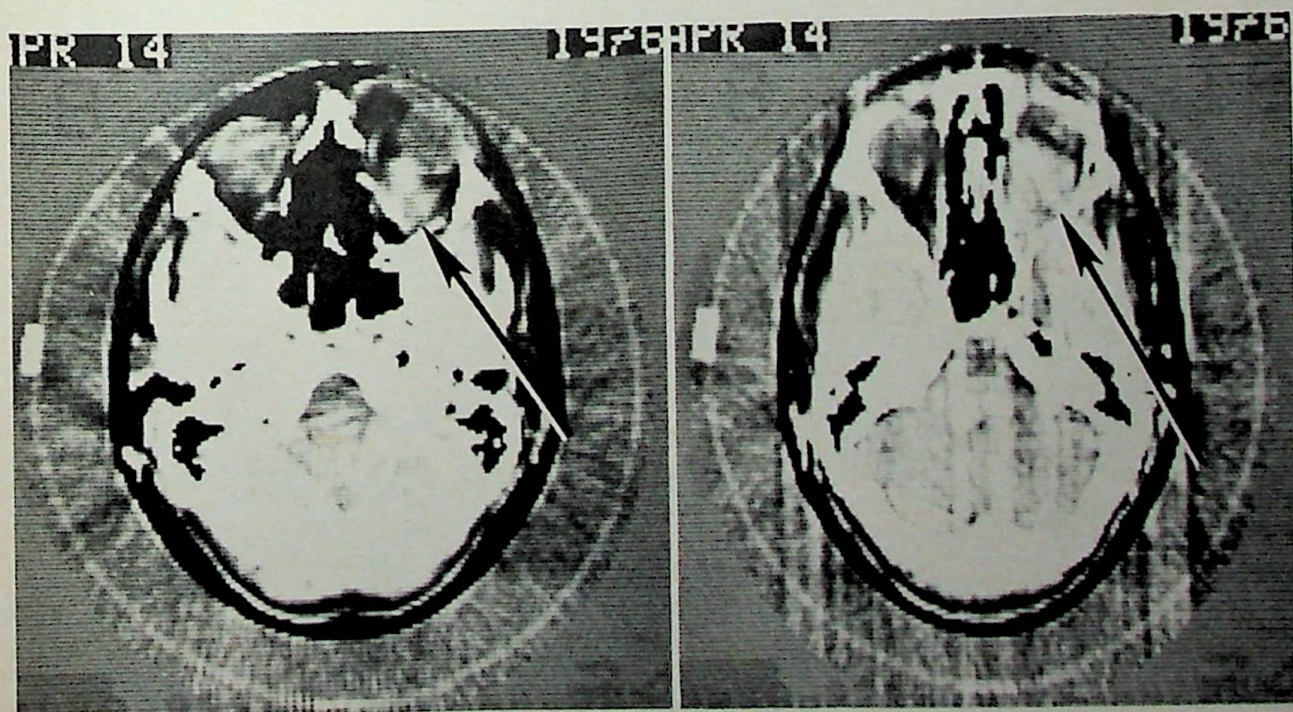
Fig. 3. Computerized transaxial tomography of orbits. *Left*, Scan through lower level of orbit. Right orbital tumor (*arrow*). Note shadow of displaced eye anterior to tumor. *Right*, Scan through upper level of orbit reveals full extent and size of tumor (*arrow*) in posterior orbit.
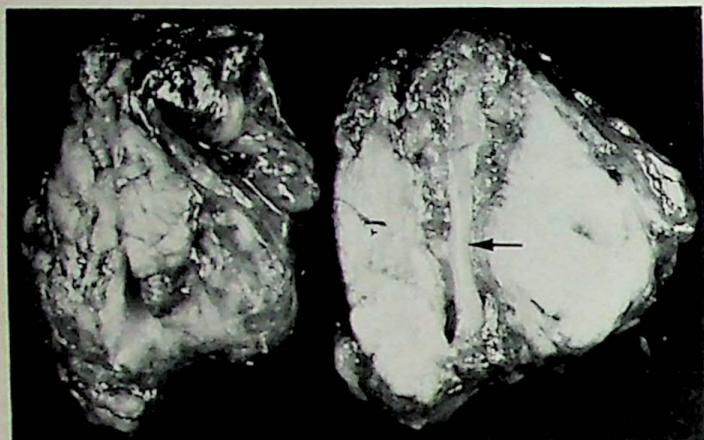
Fig. 4. Surgical specimen. Bisected tumor mass. Optic nerve (*arrow*) passes through center of neoplasm.

was then visible which filled the entire posterior portion of the orbit and extended anteriorly into the superior nasal quadrant of the orbit. Most of the tumor was situated within the muscle cone and it was possible to separate the neoplasm from the undersurface of the recti muscles and the surrounding periorbita by blunt dissection. Laterally, however, the tumor was adherent to portions of the lateral rectus muscle and adjacent periorbita, and some muscle tissue was excised to permit a more complete removal of the tumor. These adhesions were probably scar-tissue residues of the prior orbitotomy elsewhere. After the tumor was removed, an adult-sized Allen implant was placed in the orbital cavity and secured in the usual manner by uniting the cut ends of the rectus muscles across the anterior surface of the methacrylate implant. Tenon's capsule and conjunctiva were closed in layers with catgut sutures. Arrangements were made to have a prosthesis fitted in 6 weeks.

Pathologic Findings.—The tumor specimen (48 by 28 by 26 mm) was firm with an irregular lobular surface; sections showed solid, grayish-white tissue with fine interlacing strands (Fig. 4). The eye measured 23 by 25 by 21 mm with 2 mm of optic nerve. The clear cornea was 13 by 11 mm. Transillumination showed no defect. The eye was opened vertically. No abnormality of the anterior portion was noted. Apart from a prominent pale disk head, the posterior portion of the globe appeared to be normal.

Microscopy showed a meningothelial meningioma of the optic nerve sheath with focal invasion of the sclera and the formation of a tumor nodule within the choroid adjacent to the disk head (Fig 5). The meningioma cells were arranged in a solid pattern with a tendency to lobule formation. The cell boundaries were indistinct and the nuclei were large, round or oval, and vesicular (Fig. 6). The overlying retina showed degenerative changes in all layers and the optic nerve was atrophic. Sections of the temporal calotte showed choroidal folds.

DISCUSSION

In our search of the literature, we have found 17 instances[3-10] of meningiomatous invasion of the eye
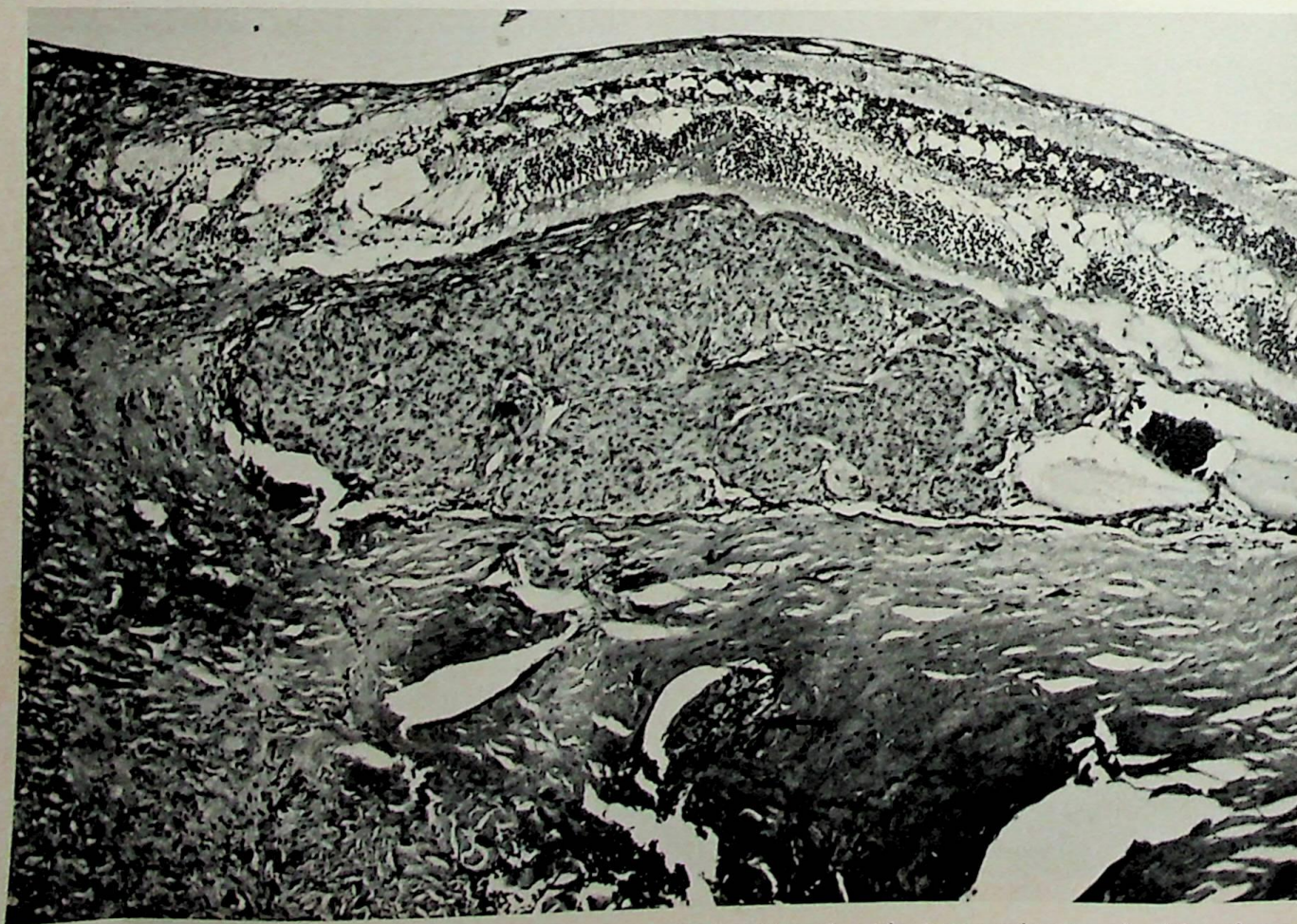
Fig. 5. Vertical section of right eye showing nodule of meningioma within choroid. *Arrow* points to scleral invasion. (Hematoxylin and eosin; ×64.)
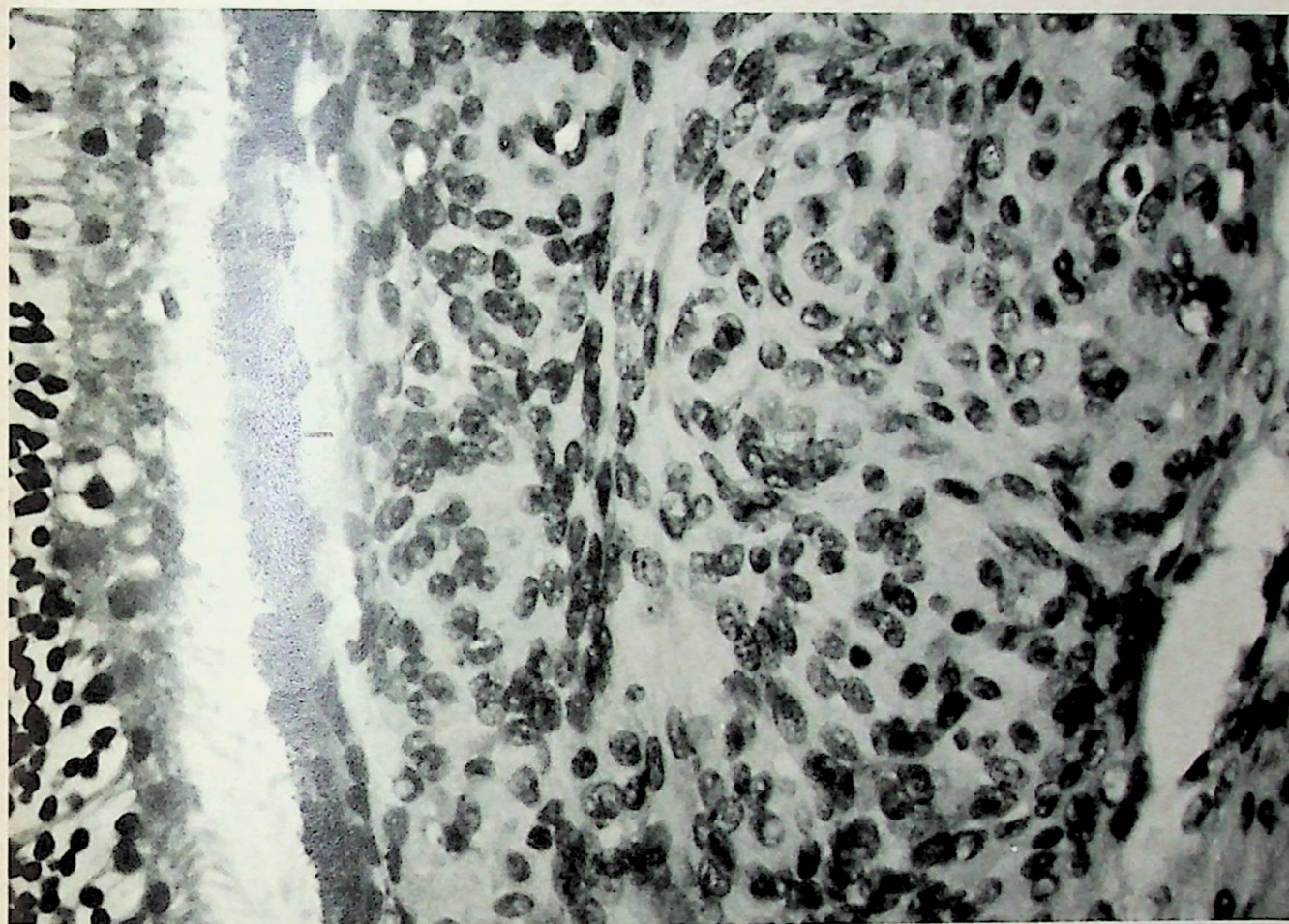
Fig. 6. Meningioma cells within choroid. Cells of meningothelial type with vesicular nuclei and indistinct cytoplasmic boundaries. *Arrow* points to retinal pigment epithelium. (Hematoxylin and eosin; ×400.)

(choroid, scleral, optic disk, or retina). Among this total, four cases were found in a review of 25 patients with verified primary intraorbital meningiomas by Karp and associates.[3] Clinical aspects of these four cases were not included in their publication. Another seven cases (six from the European literature before 1912, plus one of his own) were contributed by Hudson.[4] All remaining examples were the subjects of single case reports.

Clinical data were available in 12 of the 17 cases in the literature. The sex incidence was 3:1 females. Interestingly, four of these patients were 12 years of age or younger when originally observed because of an ocular or orbital problem, and three of these were males. The ratio of children with intraglobal extension of a meningioma among the overall total is considerably higher than the expected incidence of all types of orbital meningiomas in childhood. The higher incidence of intraglobal extension in the young may be related to the clinical observation that meningiomas are more aggressive in children. In this regard, both male patients of Martin and Schofield[7] and Dunn and Walsh[6] are noteworthy. In the first, the patient was only 3 years old when one eye was enucleated because of a large white mass involving the nasal half of the fundus and obscuring the optic disk. In the second, an 11-year-old boy, a mass was seen to arise from the temporal side of the optic disk, which came forward two to three diopters and, in total area, covered four to six times the area of the optic disk. At the time of enucleation 17 years later, the optic foramen was enlarged due to extension of the meningioma toward the chiasm. Other instances in which the tumor was visible by ophthalmoscopy before histopathologic confirmation are noted in the reports of Coston[5] and Newell and Beaman.[8] Among the 12 reports that included clinical data, the majority of the meningiomas arose from the sheath of the intraorbital portion of the optic nerve and were of the meningothelial type. Another predisposing factor among the adult patients was a long-standing history (many years) of an intraorbital mass.

As regards the mode of ocular extension of these tumors, Rodrigues and associates[9] have demonstrated

Fig. 7. Clump of meningioma cells within vessel wall (*double arrow*). *Single arrow* points to sclera. (Hematoxylin and eosin; ×100.)

by angiography and histology the presence of an optociliary shunt between the central retinal vein and the peripapillary choroid in a patient with a spheno-orbital meningioma extending into the choroid who also had massive chronic edema of the optic disk. We were unable to demonstrate such a shunt in our case despite serial sectioning; but nodules of tumor were prominent adjacent to the posterior ciliary vessels, and one vessel contained a nodule of tumor within its lumen (Fig. 7). It would appear that the points of scleral penetration of the vessels serve as a means of entry of tumor into the globe, whereas the involvement of the vessel, in this instance a vein, would appear to be secondary to invasion of its lumen. Other studies[11,12] have demonstrated invasion of the central retinal vessels.

In conclusion, primary intraorbital meningiomas in childhood and among women with a long history of proptosis or visual loss are more prone to produce ocular invasion than are meningiomas secondarily invading the orbit from intracranial sites. We suggest that the mode of penetration is along the course of the posterior ciliary vessels as they penetrate the sclera.

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Incidence of Orthostatic Hypotension in Patients With Primary Affective Disorders Treated With Tricyclic Antidepressants

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Previous studies have indicated that postural hypotension is an uncommon event when tricyclic antidepressants are used in the treatment of depression, and other studies have indicated that postural hypotension is a possible predictor of positive therapeutic response to antidepressant therapy. In this study, 20 depressed patients with the diagnosis of primary affective disorders were hospitalized and treated with tricyclic antidepressants. All patients had been without medication for at least 2 weeks before the study began. Blood pressure recordings were made after a 5-minute resting period and then followed by another reading after the patient had been standing for 2 minutes. Our findings indicate that these patients with primary affective disorders developed significant orthostatic hypotension. It is our belief that orthostatic hypotension is a significant event in patients who have primary affective disorders treated with tricyclic antidepressants, and this sign should be looked for in all patients regardless of age or the presence of significant cardiovascular disease.

Although initially thought to be quite innocuous, tricyclic antidepressants have earned a growing reputation for their sometimes noxious effects on the cardiovascular system. Orthostatic hypotension is one of these effects and is a recognized association of tricyclic antidepressant therapy in some patients. Reports of the incidence of orthostatic hypotension range from zero[1] to occurring only in patients with preexistent cardiovascular disease[2] and from occurrence in 23% of all patients treated with tricyclic antidepressants[3,4] to the opinion that it occurs regularly in certain types of psychiatric patients and may even be a useful indicator of drug activity or prognosis for response.[5,6] In view of the importance of the phenomenon, both as a potentially dangerous side effect and as a possible physiologic indicator of drug activity, and in view of the wide range of opinion concerning its incidence and significance, we attempted to study orthostatic hypotension in a group of patients receiving tricyclic antidepressants who had the diagnosis of primary affective disorder.

METHODS AND MATERIALS

Twenty depressed patients between 20 and 65 years of age, hospitalized on a private hospital general psychiatric ward, were selected on the basis of several criteria: (1) all fit the criteria outlined be Feighner and associates[7] for primary affective disorder—depression; (2) all were free of known heart disease or peripheral vascular disease, and none had ever had treatment for or been told they had high blood pressure (lack of previously noted hypertension or orthostatic hypotension was documented by existing patient records and corroborated in the patient's initial history); (3) all had gone without medication for at least 2 weeks before initiation of the study, except for 15 or 30 mg of flurazepam as a nighttime sedative in some patients.

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Three patients initially selected had improvement or resolution of depressive symptoms during the 2-week drug-free period and were not included in the study.

After hospitalization, blood pressures were taken with the patient lying supine and after standing for 1 to 2 minutes, two to five times daily, including immediately on arising and just before retiring. These pressures were recorded during pretreatment and on days 1 through 14 of treatment with tricyclic antidepressants. All patients were encouraged to be up and to partake in work activities. Remaining in bed all day was not allowed. No other medications were administered with the exception of acetominophen, milk of magnesia, or flurazepam to some patients. All patients initially received 50 mg of either imipramine or clomipramine, three times a day for the first week. During the second week, the dosage was altered within the range of 50 to 200 mg daily, according to the judgment of the clinician administering the drug. The average dose during the second week was 100 mg daily. Exceptions to this schedule occurred if the blood presssure dropped more than 40 mm Hg systolic on standing (after 2 minutes), in which case the medication was not given.

RESULTS

Of the original 20 patients, 14 of whom were women and 6 men, 1 was dropped from the study when worsening depression and suicidal concerns precipitated discontinuance of drug therapy and use of electroconvulsive treatment. One patient, due to error, had no pretreatment standing blood pressures measured. The remaining 18 patients could be fitted into three categories during the pretreatment period of blood pressure monitoring. Twelve had normal blood pressures with no abnormal orthostatic changes (definition: abnormal orthostatic change means a systolic decrease of more than 30 mm Hg, a diastolic change of 15 mm Hg, or a mean blood pressure change [changes in systolic and diastolic blood pressures added together and divided by 2] of 15 mm Hg on standing). Four had normal blood pressures but had some abnormal orthostatic changes before initiation of therapy with tricyclic antidepressants, and two patients were hypertensive (as defined by two or more consecutive blood pressure measurements exceeding 150/90 mm Hg) but had no abnormal orthostatic changes before treatment.

All patients had striking orthostatic hypotension sometime during the first 2 weeks of treatment, whether defined by systolic, diastolic, or mean pressure criteria, as shown in Table 1. If diastolic pressure, which is more significant in terms of the degree of orthostatic decrease in blood pressure, is used as the criterion, the above subdivisions disappear because none of the patients showed pretreatment orthostatic abnormalities of diastolic pressure and all

Table 1.—**Orthostatic Changes in Blood Pressure Before and After Therapy**

	Blood pressure, mm Hg					
	Systolic		Diastolic		Mean	
Patient, age; sex	Pre-Rx	Maximal change (day)	Pre-Rx	Maximal change (day)	Pre-Rx	Maximal change (day)
57; M	+4	−40 (6)	−2	−20 (6)	+1	−29 (6)
47; M	−2	−40 (7, 13)	+2	−20 (7)	0	−40 (7)
60; F	−10	−40 (7, 13)	+14	−20 (5)	+1	−23 (9)
54; F	−18	−34 (12)	−10	−32 (5)	−8	−27 (5)
42; F	−12	−60 (10)	0	−38 (10)	−5	−48 (10)
46; M	−12	−40 (6, 7, 14)	−2	−30 (6)	−7	−34 (6)
53; M	−10	−85 (8)	+2	−37 (10)	−4	−58 (7)
50; F	−10	−36 (12)	−10	−26 (7)	−10	−25 (7)
49; F	−10	−54 (10)	+8	−30 (4, 12)	−7	−34 (8)
49; F	−4	−70 (2)	+10	−40 (2)	+2	−55 (2)
43; F	−8	−60 (3)	0	−42 (10)	−3	−41 (10)
50; F	−12	−44 (3)	−1	−20 (2)	−7	−38 (5)
59; F	−32	−50 (5, 6)	−4	−38 (6)	−17	−43 (6)
62; F	−30	−55 (3)	−2	−30 (10)	−16	−39 (11)
61; F	−46	−66 (6, 8)	−10	−28 (10)	−18	−55 (11)
64; F	−24	−70 (7)	+12	−28 (5)	−15	−46 (7)
59; M	−5	−72 (11)	+6	−22 (6)	−4	−47 (6)
47; F	−10	−116 (4)	−10	−64 (4)	−10	−90 (4)
50; F	NO*	−75 (5)	NO*	−44 (5)	NO*	−62 (5)

*NO = not obtained.

had striking orthostatic decreases during the treatment period. Although the end of the first week was a common time to note more severe changes, there were no significant trends relative to when orthostatic changes were likely to occur, some patients manifesting the changes very early and others at various times throughout the 14 days. Age, sex, and drug administered did not correlate with severity of hypotension.

Four patients were asymptomatic, five had mild symptoms of slight dizziness on standing, eight had moderate symptoms of being lightheaded or dizzy while walking, and two had severe symptoms, being unable to walk.

Although the change in pulse rate was not measured routinely, it was striking that most patients did not develop a profound tachycardia even with large orthostatic changes. The pulse rate increased by 8 to 20 beats per minute when the patients stood, with systolic blood pressure changes of at least 30 mm Hg. A few patients had greater pulse responses. The changes in pulse rate should be studied further.

All patients treated did respond to somatic therapy (drug treatment or electroconvulsive treatment). One was lost to follow-up after the initial 4-week treatment with a tricyclic compound, but at the end of that 4 weeks he had not responded to therapy.

The one patient whose hypotension was so severe and uncontrolled as to necessitate cessation of medication at the end of the first week was one of the two who had hypertension in the drug-free period.

Table 1 compares the maximum orthostatic change recorded in the pretreatment period with the maximum change recorded during the first 14 days of therapy and identifies the day on which this maximal change was noted. The numbers represent the difference between the blood pressures taken while lying down and while standing, expressed in millimeters of mercury.

DISCUSSION

The relation between blood pressure and depression is increasingly recognized as complex and of growing importance to basic scientists and clinicians. The central mechanisms of both hemodynamic and affective control are being sought, along with more rational and effectives modes of treatment for disorders in both spheres. Considerable attention has been directed to the interactions between centrally acting hypotensive drugs and tricyclic antidepressants as these new antihypertensives have become more widely used and better understood.[8,9] These studies and speculations, which link blood pressure and affective disorders at a central level, are paralleled by basic research in the pharmacology of the tricyclic antidepressants which has progressively eliminated peripheral mechanisms of hypotension as important and has produced evidence that tricyclics work centrally to inhibit vasomotor tone.[10]

Such investigations lend additional credibility to Horwitz's[5] 1968 hypothesis that the appearance of orthostatic hypotension is a regular concomitant of improvement in the treatment of depression with tricyclic antidepressants, functioning as an indicator of central activity of the drug. Escobar and associates[6] have attempted to correlate the side effect of orthostatic hypotension with the diagnosis of primary affective disorder (versus secondary types), and the fact that 18 of our 19 patients with orthostatic hypotension responded to somatic treatment corroborates their work. Little else seems to have been done along these lines, and there is a remarkable absence of attention to blood pressure among the many excellent studies correlating blood levels of tricyclic antidepressants with side effects or improvement. Attempts to study physiologic parameters of treatment in general also have largely ignored blood pressure as an important indicator.[11-15]

Interest in such physiologic correlates of drug levels, drug activity, and possible drug response precipitated the present study. However, the extent and severity of orthostatic hypotension that became apparent as we recorded blood pressures have caused us to reconsider the nature and seriousness of orthostatic hypotension. Our data would indicate that it is not only the geriatric patient, the cardiac patient, or the overdosed patient who is at risk, but that essentially all patients with primary affective disorders treated with tricyclic antidepressants will have significant hypotension at some phase of their early treatment, even with what we now generally accept as therapeutic dosages. The magnitude of the decreases in the blood pressure in the patients observed is also alarming and seems far in excess of that reported heretofore. Most reports in the past have used systolic hypotension ($>$ 20 mm Hg decrease) to define orthostatic change. Diastolic and mean pressure decreases of 15 mm Hg are especially alarming in the light of a consensus that diastolic and mean hypotension of this magnitude are rarely observed in the absence of pathology and are hemodynamically worrisome in terms of adequacy of coronary and cerebral blood flow.[16]

Informal continuation of this study in less controlled patients corroborates the data from the 19 who are

reviewed here, and preliminary data indicate similar results with amitriptyline. It seems reasonable to speculate that some of the mysterious sudden deaths observed with therapy with tricyclic antidepressants may be caused by orthostatic hypotension with cardiac ischemia and resultant fatal arrhythmia, rather than by direct cardiac toxicity, in patients who are taking typical therapeutic dosages. Even if studies with much larger numbers of patients fail to substantiate the high incidence noted here, it is clear that orthostatic hypotension associated with tricyclic antidepressant therapy is a much more prevalent and worrisome phenomenon than has previously been recognized. The observation that only a minority of our patients complained of subjective orthostatic symptoms and that none had any serious sequelae associated with the objective blood pressure findings leads us to study this phenomenon further rather than to stop using tricyclic agents because of fear of orthostatic hypotension.

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Historical Vignette

Gregor Johann Mendel and the Beginning of Genetics

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Gregor Johann Mendel only dabbled in human genetics. He is said to have studied the Altbrünn register searching for problems of human inheritance.[1] He carefully monitored and recorded such characteristics as hair growth, hair color, and stature among members of his own family. He sometimes attended postmortem examinations at a local hospital, and he often discussed medical principles with his two nephews when they visited him. He obviously approved of medicine as a profession because he paid for the medical education of his nephews and encouraged them in their studies. Despite Mendel's casual exposure to medicine, the fundamental laws of genetics that he formulated in the 8 years before 1865 have had a great impact on the whole field of medicine.

Mendel's greatest contribution to science was to initiate a movement to replace the "blending theory" of inheritance with a particulate one. From the results of his experimentation with the edible garden pea, he formulated the following principles of genetics: that hereditary characters are determined by "elements (today these are called genes); that there is a pair of elements for each character; that the elements for each character segregate during gametogenesis; and that when the male and female gametes fuse to form the zygote, the paired status of these elements is restored. This has become known as Mendel's law of segregation. Mendel also discovered the principle of dominance and coined the terms "dominant" and "recessive" used in today's genetic terminology to describe the relative expression of genes. Mendel formulated the genetic law that members of any pair of genes segregate independently of others. We now realize that it is actually the chromosomes that segregate and not the individual genes, but Mendel's principles are still valid when applied at the chromosome level.

Modern geneticists label any characteristic, normal or abnormal, that segregates in a manner described by Mendel as exhibiting a mendelian pattern of inheritance. In clinical practice there are nearly 600 genetic disorders that are known to show dominant expression, about 450 that are recessive, and over 90 that are X-linked; all are examples of mendelian inheritance.[2] About another 1,000 diseases are currently suspected to be inherited in a mendelian fashion. Because Mendel's laws are fundamental to life, their importance permeates all fields of biology and medicine, not just medical genetics. The intent of this paper is to review the life of Gregor Mendel and his epoch-making experiments with the garden pea.

SYNOPSIS OF HIS LIFE

Johann Mendel[1,3-8] was born in 1822 in Heinzendorf, Austria—today Hynčice, Czechoslovakia. There is some conflict about his exact birth date, because he always celebrated the occasion on July 22, St. Magdalen's Day; but in the Petersdorf parish register and on his baptismal certificate it is designated as July 20. His father, Anton, served for 8 years as a soldier during the Napoleonic Wars and, thus, traveled extensively. This experience proved beneficial to Anton when he set about his life-long business of operating the farm that he inherited from his father. Johann's mother, Rosine, was the daughter of Martin Schwirtlich, who was a village gardener by trade. Rosine and Anton married in 1818 and, after the death of two infant girls, the couple produced Veronica in 1820, Johann in 1822, and Theresia in 1829. Johann loved his family greatly, but throughout his life he was particularly fond of his good-natured younger sister, Theresia. She must have loved him dearly as well, because she gave up part of her dowry to help defray part of Johann's education. The two corresponded often during their lives and Johann helped pay for the medical education of two of her sons.

While a boy, Johann was instilled with the spirit of gardening. His maternal grandfather was a professional gardener, as were a number of his other ancestors. From his father he learned about farming and became particularly interested in the family's fruit tree orchards. During his elementary education,

Johann was influenced by the village vicar, whose name was Schreiber and who taught natural science and encouraged the cultivation of fruit trees. Johann retained his fondness for fruit growing long after all his practical interest in botany ceased.

In his elementary education, Johann demonstrated exceptional academic ability, which was recognized by Schreiber and the village schoolmaster. Thus, his parents sent him to the Piarist secondary school in nearby Leipnik (today Lipnik) in 1833. One year later they sent him to the Gymnasium in Troppau (today Opava) where he studied for 6 years until 1840. At the Gymnasium, Johann was considered one of the best pupils in his class, graduating *primae classis cum eminentia*. In 1838, 2 years before Johann graduated from the Gymnasium, his father suffered serious injuries from an accident and had to retire from farming. Because Johann did not wish to become a farmer, Anton turned his farm over to his son-in-law, Alois Sturm, who had married Johann's elder sister, Veronica. Consequently, Johann's parents could no longer pay for his school expenses. Thus, at the age of 16, Johann had to fend for himself. He labored hard to continue his schooling and at the same time earn a meager living by tutoring students. The physical and mental strain on Johann became so serious that he became ill and had to interrupt his studies for several months. After recovering, he still managed to complete his secondary studies with excellent records. In 1840, Johann enrolled in the philosophy course at the University of Olmutz (today Olomouc) in preparation for higher studies. Here, his efforts to earn a living by tutoring failed miserably because he lacked references. Again he became ill from the distress and frustration of the situation and he returned home to spend a year convalescing with his parents.

Johann was not one to give up his studies easily. He accepted his sister's offer to provide him with a portion of her dowry to help him return to Olmutz and complete the 2-year philosophy course. At Olmutz he was introduced to the principles of physics and mathematics, which later were to serve him well in his research. His physics professor, Friedrich Franz, played a decisive role in Johann's life. Franz had taught for 20 years at the Philosophical Institute in Brünn (today Brno) while living in the Altbrünn monastery, where he naturally became acquainted with many members of this monastic community. In the same year that Johann graduated from the Philosophical Institute at Olmutz, Professor Franz received a request from the monastery for names of pupils who might be suitable candidates for membership in this Augustinian monastery. Mendel had developed an enormous distaste for hard labor and on graduation decided to select a profession which would spare him any strenuous exertion. He asked for advice from Professor Franz. Since Franz thought highly of Mendel, he recommended him for admission into the Altbrünn monastery. Mendel was accepted and, on Oct. 9, 1843, he entered the monastery as a novice and assumed the name Gregor, which he used thereafter before his baptismal name.

Monastery life suited Mendel's ambitions perfectly. The eminent incumbent prelate, Cyrill Franz Napp, had improved the monastery to the point where it had become solvent, supported by the income of its estates. Thus, Mendel, like the other monks, was free from financial worries. Furthermore, because the monastery itself was a place of learning and scientific endeavor, Mendel was at liberty to pursue his studies. Prelate Napp was a distinguished leader; he promoted studies to improve agriculture in the area and encouraged his fellow monks to experiment with plants in the monastery gardens. Shortly before Mendel arrived at the monastery, Pater Aurelius Thaler died. This man had become a well-known botanist in the region and had established a large herbarium and botanical garden at the monastery. Prelate Napp encouraged Mendel to take charge of the herbarium and gardens. He happily accepted the responsibility. In his early experiments, Mendel was guided and influenced by Matthew Klácel, a local teacher of philosophy and well-known Brünn botanist. Klácel was particularly interested in plant variation, heredity, and evolution.

In 1845, Mendel began a 4-year study of theology at Brünn Theological College. During this time he also attended classes at the Brünn Philosophical Institute, as did many of his fellow monks. At the Philosophical Institute he heard lectures on agriculture by Professor Franz Diebl, an expert on artificial pollination as a method in plant experimentation. Both Diebl and Prelate Napp were among the organizers of the Congress of German Agriculturists at Brünn in 1840. Mendel attended the meetings of the Congress and heard botanists discuss hybridization experiments with fruit trees. In 1847, a number of priests at the monastery died, making it difficult to conduct daily religious services. Thus, Prelate Napp recommended Mendel for priesthood, even though he still had 1 year of theologic study to complete. On his 25th birthday, July 22, 1847, Gregor Mendel was ordained subdeacon; on August 4 he became a deacon, and 2 days later, a priest. On June 30, 1848, Mendel graduated from the Theological College and a month later became chaplain to the parish served by the monastery.

His primary duty was to see to the religious needs of poverty-stricken patients in a nearby hospital. Mendel was a very sensitive man and could not stand the sight of suffering. He became very depressed with his duties, almost to the point of illness. Prelate Napp understood and relieved him of his hospital duty.

Napp then sent Mendel, as a substitute teacher, to the grammar school at Znaim (today Znojmo), where he taught elementary mathematics and Greek. Mendel lacked the proper educational credentials required to teach but, like other priests who taught, was presumed to be fit for such a post simply because of his Order. Mendel enjoyed teaching and impressed both his colleagues and pupils with his abilities. Consequently, the headmaster recommended Mendel for the examination for teachers of natural science which, if he passed, would permit him a regular appointment. Unfortunately, Mendel failed the examination; though he did well in physics and meteorology, he did poorly in geology and zoology. The examiners attributed the failure to Mendel's lack of a university education. Accordingly, Napp sent Mendel to the University of Vienna to procure this education.

At the university, Mendel attended lectures on physics by Doppler and on construction of physical apparatus by Andreas von Ettinghausen. He also took courses in paleontology, botany, zoology, and chemistry and was particularly interested in plant physiology, taught by Professor Franz Unger. Unger was famous for his research on fossil plants, the influence of soil on plant development, and the causes of plant variation. In his lectures, Unger emphasized the role of sexual reproduction as a primary source of variation in cultured plants. Mendel also became acquainted with Stuttgart's massive work involving 10,000 separate experiments with hybrids obtained from 700 different species.

On returning to Brünn, Mendel was appointed substitute teacher at the Brünn Technical School and again received praise as a teacher from his colleagues and pupils. He still enjoyed teaching, although his job was not easy. His classes were large, containing over 100 students, and he had to make the best of what little supplies he was given. In 1856, shortly after his return from Vienna, he began experimenting with garden peas and soon perfected the task of artificial pollination. At the same time, he prepared for his second university examination to teach natural sciences. He began the test in May of 1856, but unfortunately broke down during the test because of psychologic stress and returned to Brünn, leaving the test incomplete. As a consequence, he became so ill that his father and uncle traveled to Brünn to come to
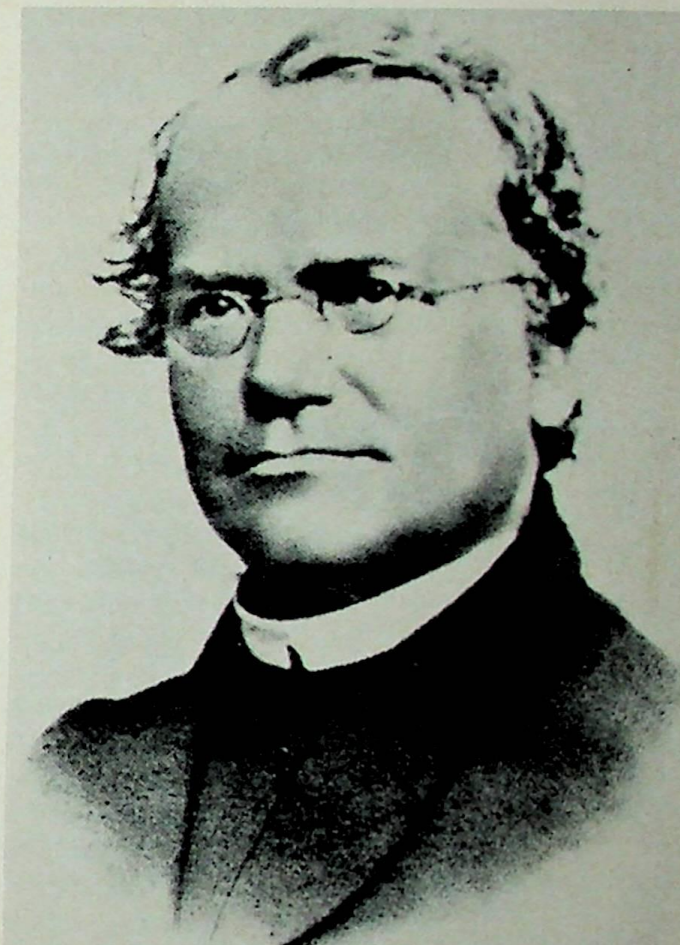
Fig. 1. Photograph of Gregor Mendel taken in 1862 during the time when he was teaching and experimenting with peas. Photograph is known as "The Handsome Mendel."

his aid. This is the only time his father came to the monastery. After recovering, he never again sought further degrees and was content with being a substitute teacher until 1868, when he retired from teaching to become prelate of the monastery. But the time between his recovery and 1868 proved to be Mendel's most productive to mankind, for it was during this period that he experimented and formulated his now famous laws of genetics (Fig. 1).

After Mendel was elected prelate of the monastery, his official duties sapped his time. Throughout his entire life Mendel was friendly and outgoing, eager to become involved. Thus, he actively participated in many organizations, devoting less and less time to his research. In 1870 he became a member of the Central Board of the Agricultural Society and was responsible for the distribution of grants to promote farming. As a member of the board he became involved in the organization of the first statistical service for agriculture, reported on the scientific literature, and served as coeditor of the society's journal.

From 1863 on he was a member of the Brünn Horticultural Society and in 1870 he joined the Society of Apiculturists and heavily influenced the development of both of these fields.

Mendel had liberal political views and publicly supported nominees of the victorious Liberal Party in the election of 1871. Unfortunately, when the new party took office it issued a law requiring monasteries to contribute large sums of money to the national religious fund. Mendel stubbornly refused to comply, arguing that the government had no right to tax monasteries. After 1875 he became entangled in a lengthy confrontation with the authorities about this issue. Eventually the government sequestered much of the monastery land to pay for the delinquent taxes. However, Prelate Mendel was an influential fellow and the Liberal Party did not wish to lose his support. So, in a final effort to retain his support, the party gave Mendel a position on the board of directors of the all-important Moravian Mortgage Bank in 1876. In 1881, he even became its chairman. But Mendel remained obstinate and continued to challenge the right to tax the monasteries. By this time he was ill with chronic renal disease. Progressive edema and incipient uremia handicapped his activities. The burden of his political problems probably hastened his death on Jan. 6, 1884, at 62 years of age.

No one at Mendel's funeral was aware of the great impact that his work would have in the future. Mendel's popularity at the time was probably best stated by a resident of Brünn 6 years before Gregor's death. The Brünn resident told a traveling seed salesman, C. W. Eichling, that

> . . . while *der herr Abt* was one of the best beloved clerics in Brünn, not a soul believed his experiments were anything more than a pastime, and his theories anything more than the maunderings of a charming putterer.[9]

HIS WORK

When Mendel recovered from his depression after failing his second teaching examination, he returned to his important experiments with peas in the small monastery garden (7 by 35 meters). In the 8 years between 1856 and 1863, Mendel planted and tested at least 28,000 pea (primarily *Pisum sativum*) plants, systematically recording the nature of seven contrasting characteristics of the seeds and plants. These characteristics included tall versus short plants, round versus wrinkled peas, yellow versus green peas, and four others. Mendel's experiments stemmed from his hypothesis that the basis of heredity was particulate, not a blending phenomenon as most people of his era thought. He believed that each plant characteristic was caused by the effect of an "element" and that each cell contained a pair of "elements" for each trait.

Mendel cultivated pea plants that grew over 6 feet tall, which, when self-fertilized, always produced only tall plants. Similarly, he cultivated pure-breeding short pea plants only 1 foot in height. By artificial fertilization, Mendel crossed tall with short pea plants and found that in the first generation all the resulting hybrid plants grew tall. Mendel called the tall characteristic *dominant* and the short trait, which was latent in the first-generation hybrids but which reappeared in the subsequent generation, he termed *recessive*. Mendel believed that the "elements" determining each character segregate in the process of forming the germ cells of the hybrids without influencing each other, such that every pollen or egg cell randomly contains one "element." Fertilization of an egg with a pollen grain reinstituted the two-element state.

Mendel always designated the element of a dominant trait by *A*, the recessive trait by *a*, and the hybrid form by *Aa;* this is a notation system that is followed by modern geneticists. Thus, when the F_1 hybrids were self-fertilized, he predicted that the constitution of the second-generation hybrids could be denoted by the formula $A + 2Aa + a$. Thus, in the case of plant height, he expected approximately three tall plants to every short plant. His F_2 results, indeed, showed that both parental forms did reappear and included 787 tall plants and 277 short plants, which is 2.84:1. He also obtained similar results for the other six pairs of contrasting traits he studied. After 1900, this segregation of parental traits was referred to as Mendel's law of segregation or Mendel's first law. Mendel conducted other experiments involving three contrasting traits and found that the elements responsible for each trait segregated independently of each other. Today this is known as Mendel's law of independent assortment or Mendel's second law.

Mendel was 44 years old when he presented his work before his friends at the Society of Naturalists in Brünn. He presented his work in two parts; the first lecture was on February 8 and the second on March 8, both in 1865. Unfortunately, no one who attended these lectures understood what Mendel had said. The minutes of the proceedings show that there were no questions and there was no discussion following his presentation. A year later Mendel was asked to publish his work in the society's proceedings. Although Mendel had done an enormous amount of work, he thought his results were inconclusive and that more research was needed. But he reluctantly accepted the publication offer and then carefully reexamined

his calculations and submitted his now classic paper for publication.[8,10,11]

At about the time that Mendel became prelate, he began communicating with the famous botanist of the era, Carl von Nageli, of Munich. Mendel hoped Nageli would appreciate his work and assist him in the investigation of other plant species in an attempt to test the universality of his observations. Unfortunately, Nageli was a self-centered individual and paid little attention to poor Mendel's paper. Instead, Nageli attempted to enlist Mendel's aid in studying hereditary patterns of plants in the hawkweed genus, *Hieracium*. Mendel acquiesced and did experiments with various hawkweed species for several years. This turned out to be a waste of his time. These plants were not easily available to Mendel and artificial fertilization was very difficult because of the small and numerous florets which make up their influorescence. However, Mendel was an expert microscopist and did manage to use artificial fertilization successfully in his *Hieracium* experiments.[12] The chief problem with hereditary studies involving hawkweed species is that most of them reproduce primarily by parthenogenesis and only partially by sexual reproduction. Any offspring that originate from parthenogenic processes are actually shoots from the parental plants and their phenotype differs little from that of the parent. Mendel could not have been aware of this phenomenon among the hawkweed. It was discovered after his time. With great labor, Mendel systematically crossed a multitude of different hawkweed species but produced relatively few hybrids and did not obtain his expected ratios. He published his work on *Hieracium* in 1870 in the Proceedings of the Brünn Natural History Society. But his hopes of finding confirmation of his principles of inheritance in plants other than peas were shattered. Thus, in the absence of scholars to appreciate and further confirm his results, and because of his frustrations with the hawkweeds, for all practical purposes he abandoned his study of inheritance with plants during his later years.

Mendel turned his research attention to meteorologic studies, to experiments with bees, and to fruit-tree growing, and he contributed greatly to each of these fields. As a meteorologist, Mendel discovered the principle of tornado formation and he published his concept in the Proceedings of the Society of Naturalists in Brünn. Unfortunately, this work did not receive immediate attention from the scientific world and was lost in the literature until 1921. Then the paper was recovered by modern meteorologists who became disappointed to learn that they were not the first to describe the correct principle of tornado formation.

Mendel's ideas about inheritance were far ahead of his time and the quality and extent of his work attest to his brilliance, perseverence, and industry. His approach, methods, and results were all novel compared with those of his predecessors. He reduced a complex problem of crossing plants into a simple, exact analysis, leaving little to chance. He selected peas for experimentation only after a thorough review of the literature and numerous preliminary experiments. He carefully checked and rechecked the purity of his parental forms and then hybridized the pure breeding plants. He chose to follow only those few characteristics in which there was a clear distinction—for example, tall versus short. Because he dealt with only seven characteristics, Mendel was able to perform logically and to comprehend all combinations of hybridization experiments. His work involving large populations was new and allowed him to subject his data to mathematical treatment. He used statistical analysis to extract his now well-known laws of heredity and his great powers of abstraction enabled him to recognize the basic genetic principles operating in nature.

Mendel's work lay dormant until 1900 when, within a 2-month period, Hugo de Vries of Amsterdam, Carl Correns of Tubingen, and Erich von Tschermak of Vienna independently arrived at exactly the same conclusions as Mendel.[13] Each of these eminent investigators found Mendel's paper in their search of the literature in preparation for publication of their work. Mendel owes each of these men a great debt of gratitude, for they brought his work to the attention of the scientific world and so are directly responsible for the widespread fame that has come to Mendel today. Those who have unkind thoughts about Nageli for misleading Mendel in his research might find some comfort in knowing that Carl Correns was once a student of Nageli, so indirectly Nageli also proclaimed Mendel as a great scientist. Today there is a large marble statue of Mendel at the monastery in Brno, and the monastery itself has become his shrine. But the greatest honor of all for Mendel must surely be his general recognition by the scientific world as the Father of Modern Genetics.

This would seem a logical place to end this article: the reader would be satisfied that Mendel had received his just rewards and posthumously had been given a proper place in science's Hall of Fame. But even in death Mendel has encountered misfortune. In 1936, Robert Fisher [14] subjected Mendel's data to

statistical analysis and found that they were too close to theoretical prediction to have occurred by chance alone. This brought charges that Mendel had deliberately biased his data. Sewall Wright[15] confirmed Fisher's statistical findings but he tempered the blow to Mendel's reputation. He states that Fisher did not allow "... enough for the cumulative effect on χ^2 of a slight subconscious tendency to favor the expected result in making tallies." Deliberate falsification of data would seem grossly out of character for Mendel, but the fact remains that his data probably were biased. It is possible that his assistant, in his eagerness to make his master happy, counted peas in a manner that the expected 3:1 ratio would be obtained. Mendel himself may have unwittingly biased his data. His approach was new; thus there were no similar previous studies to which he could refer in designing his experiment to obtain completely objective data. Although this charge is serious and disconcerting, we may never know exactly what happened. Therefore, it seems more important to remember that Mendel's hypotheses have evolved into important genetic laws and that these laws have greatly advanced man's knowledge of biology.

ACKNOWLEDGMENT

I would like to thank Dr. Claude Welch, Macalester College, for the loan of his copy of *Iconographia Mendeliana* and for sharing the experiences of his visit to Mendel's home in Brno. Dr. Earl Gritton, an agronomist from the University of Wisconsin in Madison, provided kind assistance on Mendel's work with peas. Dr. Vítězslav Orel, head of the Mendelianum in the Moravian Museum in Brno kindly supplied me with vital literature about Mendel's life.

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Editorials

Health Care Cost
The Role of the Physician

Physicians traditionally have been concerned principally with providing medical care of the highest quality and to a much lesser extent with the cost of that care. Indeed, most medical school curricula have not dealt significantly with the cost of health care in the past. Rather, physicians have been taught from earliest times to do all they possibly can for their patients without considering cost. This philosophy has evolved from the creed that a physician should minister to all patients with maximal skill and resources irrespective of the patients' ability to pay. This tenet continues to be held today as strongly as ever. In the past the only result of this philosophy had been that physicians or hospitals were not reimbursed for their services. This created little interest and certainly no national concern. What has changed in this equation is the fact that more and more people are able to pay either personally or through third-party reimbursers. As inflation, a scientific base, and technologic advances have added to costs, there has been a noticeable impact on society at large by the physician's traditional philosophies.

There can be no doubt that health care costs are increasing at a rate that, if left unchecked, will create increasingly uneven levels of care in our society, which is one that strives for egalitarianism. In considering the causes for the rapid increases in costs, it is easy for varying interests to point selectively to private and governmental health insurance, inefficient hospitals used too infrequently, physician abuse of the system, governmental largesse, malpractice insurance, labor programs, technologic advances, inflation, an increasingly older population, and so on. As individual physicians view these potential causes and note that health programs consumed $135 billion, or 8.3% of the gross national product, in 1975, our first impulse is to give up in frustration and insecurity and secondly to fight for the status quo. Such reactions certainly accomplish nothing for the public good or for the medical profession. Compassionate and thoughtful physicians must work to seek solutions for all of society.

Lewis,[1] in an analysis of the 1977 federal budget and health policy, noted that Governor Brown of California may have been expressing a new philosophy of government and its role when he said, "We are entering an era of limits. In place of a manifest economic destiny, we face a sober reassessment of new economic realities; and we all have to get used to it." Indeed, a recent Harris survey[2] showed that the American people have begun to show a deep skepticism about the nation's capacity for unlimited growth and are wary of the benefits of continued economic growth. Whether or not these economic concerns will be translated into changing expectations of health care is a moot point. Nevertheless, all of the foregoing matters suggest to physicians that the time has come for us to be very much concerned about health care costs. We must increasingly weigh the resources utilized in trying to be helpful to patients against the significant benefits that can be expected therefrom.

Many groups within the health-care delivery system are anxious to assume responsibility for doing something about the costs of medical care and thus to gain the leadership role in the system. Government itself has much at stake and is assuming increasing control. One could feel better about this role of government if it were a bit more effective in controlling its own costs. Traditionally, leadership in the delivery of health care and practice of medicine has been the responsibility of the physician. Indeed, very little can be done to control costs or significantly change the system without the cooperation of physicians. What the solution requires, however, is not cooperation of physicians but assumption of an aggressive leadership role and the development of programs by physicians. Societal problems are complex today, and when individuals as such try working toward solutions they are often frustrated. However, solutions to the present problems require each of us as individuals to make a beginning in our practices and to influence organized medicine, professional medical societies, subspecialty medical and

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surgical societies, and large institutions such as clinics and medical schools to take the lead in seeking solutions. Any solution also will require that consumers of medical care change their expectations of that care. Physicians again will need to play a leading role in guiding the expectations of society in such changes.

W. Eugene Mayberry, M.D.

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Dr. Mayberry is Chairman of the Board of Governors of the Mayo Clinic—Ed.

Nosology of Pulmonary Vasculitides

All that wheezes is not asthma, nor are all necrotizing granulomatous pulmonary vasculitides Churg-Strauss syndrome (see page 477).

Pulmonary vasculitis, liberally defined, means an inflammation of the vascular wall in the lungs, irrespective of the underlying cause, known or unknown. The qualifying word *granulomatous* is added when the inflammatory infiltrate is rich in lymphocytes, plasma cells, and histiocytes, often accompanied by multinucleate giant cells, and assumes a nodular pattern. Should fibrinoid necrosis of the vascular wall or the surrounding parenchymal tissue, or both, become a regular feature, the vasculitis is characterized as *necrotizing.* The preponderance of eosinophilic granulocytes in the inflammatory exudate, as an additional histopathologic marker, may be one medical taxonomist's delight and another's nightmare.

The cause and pathogenesis of most clinicopathologic entities of pulmonary vasculitis are unknown. The exceptions are infective pulmonary arteritis and pulmonary arteritis due to irritating embolic material, so designated because the inciting microorganisms and foreign substances can be identified. To these may be added granulomatosis and arteritis of the lungs associated with lipoid pneumonitis. The source of the lipid material may be intrinsic (from the breakdown of host tissue) or extrinsic (such as nasal drops containing liquid petroleum or aspirated castor oil).

Less well defined but nevertheless constituting a special group of pulmonary vasculitides is arteritis occurring in severe forms of pulmonary hypertension. Pulmonary hypertension is considered to be present when the resting systolic/diastolic pressure in the pulmonary artery exceeds 30/15 mm Hg or when the mean pulmonary arterial pressure exceeds 25 mm Hg.

Six clinicopathologic patterns of hypertensive pulmonary vascular disease have been described by Wagenvoort.[1,2] They are (1) vasoconstrictive pulmonary hypertension, as represented by primary (idiopathic) pulmonary hypertension and congenital heart disease with a shunt between the systemic and pulmonary circulations; (2) chronic or recurrent pulmonary thromboembolism; (3) increased pulmonary venous pressure, as in mitral valvular disease; (4) pulmonary hypertension in chronic hypoxia, whether due to parenchymal lung disease or to living at high altitude; (5) vascular changes due to diminished pulmonary blood flow, as in tetralogy of Fallot; and (6) pulmonary veno-occlusive disease.

Rarely, pulmonary hypertension and angiitis may be observed in patients with severe hepatic injury, such as cirrhosis. This, together with pulmonary hypertension and angiitis induced experimentally by feeding *Crotalaria sagittalis* to animals and the speculative causal relationship between pulmonary hypertension and certain anorexigens (such as aminorex fumarate) in man, is highly suggestive of a humoral mechanism in the pathogenesis of dietary pulmonary hypertension.[3]

All of the above have two features in common—namely, the inflammatory changes are confined to the pulmonary vasculature and their occurrence can be explained although they are not perfectly understood.

One is still left with an even larger and motley group of pulmonary vasculitides, some of which are peculiar to the lungs whereas others represent pulmonary manifestations of a systemic disease. In this regard, polyarteritis nodosa with pulmonary involvement and vasculitides of the various forms of connective tissue disease (rheumatic-rheumatoid disorders, systemic lupus erythematosus, scleroderma, dermatopolymyositis, and the like) are prime examples, and the families of pulmonary angiitis and granulomatosis are other examples. These pulmonary vasculitides defy a rigid classification by their own inconsistency in the size and number of vessels involved, histopathologic characteristics, and the frequency of pulmonary involvement in any given systemic disease. But perhaps the single most important reason for the difficulty in formulating a satisfactory scheme of classification resides in our ignorance of the cause and the pathogenesis of

granulomatous pulmonary vasculitides, of which Churg-Strauss syndrome, or allergic granulomatosis and angiitis, is one such entity.

In his Amberson Lecture, Liebow[4] gave a comprehensive review of pulmonary angiitis and granulomatosis and defined five varieties on the basis of histologic characteristics and some features of natural history: (1) classic Wegener's granulomatosis, (2) limited forms of Wegener's granulomatosis, (3) lymphomatoid granulomatosis, (4) necrotizing sarcoid angiitis and granulomatosis, and (5) bronchocentric granulomatosis. In Liebow's view, any implication that these conditions are necessarily "variants" of the same disease is unwarranted, since cause and pathogenesis are both unknown. On this premise, the reason for the noninclusion of Churg-Strauss granulomatosis by Liebow is unclear.

Chumbley and co-workers, in this issue of the *Proceedings*, emphasize, as did Churg and Strauss, the similarities between allergic granulomatosis and angiitis and polyarteritis nodosa with pulmonary involvement, Wegener's granulomatosis, and Löffler's syndrome (eosinophilic pneumonia). They vary from each other only in the intensity and extent of the changes produced. All of these disorders are currently considered to result from a hypersensitivity immune reaction of the Arthus type in which the lung is one of the principal target organs. Fienberg[5] referred to the whole group of disorders as "pathergic granulomatoses"; the term "pathergy" may be defined as any lesion caused by an altered immune reactivity of blood tissues.

Since allergic granulomatosis of the prostate has been observed occasionally in chronic asthmatic patients,[6] its occurrence in Churg-Strauss syndrome is, therefore, not surprising. Löffler[7] had earlier drawn attention to the association of eosinophilic epididymitis in a chronic asthmatic patient who had also shown fine nodular opacities scattered throughout his lung on roentgenograms.

Although the vascular lesions of noninfective granulomatous angiitis of the central nervous system,[8] as the name implies, occur selectively in the central nervous system, there has been a report of one patient in whom granulomatosis also occurred in the lungs.[8] Similarly, pulmonary involvement was observed in the recently described entity of disseminated visceral giant cell angiitis,[9] in which granulomatous inflammation of extracranial arteries and arterioles (and venules in some instances) of multiple visceral organs was the common histopathologic denominator.

Table 1.—**Classification of Pulmonary Vasculitides**

I. *Vasculitides of known or speculative cause and confined to the lungs*
  - Infective arteritis (bacterial, fungal)
  - Arteritis due to irritating embolic material (cotton, gauze, *Schistosoma*)
  - Arteritis of pulmonary hypertensive vascular disease
    - Vasoconstrictive (for example, primary or idiopathic pulmonary hypertension)
    - Recurrent thromboembolism (for example, secondary pulmonary hypertension)
    - Increased venous pressure (for example, mitral valvular disease)
    - Chronic hypoxia (for example, pulmonary fibrosis, high-altitude habitat)
    - Diminished blood flow (for example, tetralogy of Fallot, pulmonary atresia)
    - Pulmonary veno-occlusive disease
    - Dietary (for example, cirrhosis of liver, anorexigens)
    - Experimental (injection of methylcellulose, ingestion of *Crotalaria*)

II. *Vasculitides of pathergic granulomatoses of unknown cause*
  - Churg-Strauss granulomatosis
  - Classic Wegener's granulomatosis
  - Limited form of Wegener's granulomatosis
  - Lymphomatoid granulomatosis
  - Necrotizing sarcoid granulomatosis
  - Bronchocentric granulomatosis

III. *Vasculitides as manifestations of systemic diseases of unknown cause*
  - Polyarteritis nodosa
  - Rheumatic-rheumatoid disorders
  - Scleroderma (progressive systemic sclerosis)
  - Systemic lupus erythematosus
  - Dermatopolymyositis
  - Löffler's syndrome, hypereosinophilic syndrome
  - Takayasu's arteritis (affecting the elastic pulmonary arteries only)
  - Noninfective granulomatous angiitis of the central nervous system
  - Disseminated visceral giant-cell angiitis

We have considered, thus far, the various types of angiitis occurring in the lung parenchyma. Vasculitis of the pulmonary artery and its main lobar branches is exceedingly rare if not totally unknown. However, evidence is accumulating to indicate that Takayasu's arteritis occurs in the major pulmonary arteries much more commonly than is generally appreciated.[10]

For now, a classification of pulmonary vasculitides (Table 1) must of necessity be arbitrary. One hastens to add that it is possible to find fault with any and every proposed scheme of classification so long as only meager clues are available on the cause and pathogenesis of what seems to be an inordinate variety of pulmonary vasculitides. One justification for having such a classification, however imperfect, would be the

assumption that it is more desirable to deal with an orderly chaos than with just chaos.

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Letters

Saccharin

The editorial by Dr. Arnold Brown[1] in the June 1977 issue of the *Proceedings* is timely and apropos for those of us who are free to make a choice between sugar and saccharin. But is society to abandon those diabetics who desire a cold "Coke" (diet, that is) and eliminate their only choice, which is to drink a diet beverage or not to drink at all? And this would be done on the basis of inconclusive evidence.

Although the applicable laws may be different, the government must recognize the glaring inconsistency of the proposed ban when compared with the known carcinogenicity of cigarettes. If cigarettes require a mere warning label and the choice to smoke or not to smoke continues to exist, why not the same for saccharin (at least until a possibly safer sweetener is found)?

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Dr. Brown Replies

I sympathize with the problem described by Dr. Zweig concerning the desire of diabetics to have diet soft drinks available to them. The decision by the FDA will have to consider the benefits to diabetics of such drinks and the risks—not only to diabetics but also to the significant portion of the population who are not diabetic but who also drink diet soda. If they perceive the risk to be greater than the benefit, then diabetics will have to adapt in some way to the absence of such beverages. The basic problem is the interpretation of the data that are available on the carcinogenicity of saccharin.

The "glaring inconsistency" mentioned by Dr. Zweig between the action being considered for saccharin and the government's attitude toward cigarettes is just that. It is an irrational position based entirely on political grounds. The government's policy on tobacco represents the will of Congress. That policy will not change until the Congress takes a different view of its responsibilities.

Ephraim McDowell

I would like to add an ironic postscript to the historical vignette on Ephraim McDowell, "The Father of Ovariotomy," in the February 1977 issue of the *Proceedings*.

In 1830, at the age of 58, Dr. McDowell suffered an attack of what was called inflammatory fever, a disease whose onset was signaled by an acute attack of pain and nausea followed by fever. Thus, it is not unlikely that this pioneer in abdominal surgery succumbed to acute appendicitis.[1]

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New York, New York

REFERENCE

1. Gross SD: Memorial oration in honor of Ephraim McDowell, "The Father of Ovariotomy." *In* Lives of Eminent American Physicians and Surgeons of the Nineteenth Century. Edited by SD Gross. Philadelphia, Lindsay & Blakiston, 1861, pp 207-230

PSRO

Because I am sure that all editors, young and old, enjoy hearing from those who are reading their material, I am submitting my vote for the new format of the *Proceedings*. It is an affirmative vote. I like the bright cover. You will be happy to know also that the wrapperless journal reached me with absolutely no damage.

I should like to add that I also enjoyed the PSRO editorial in the July issue very much. The backing and filling process in trying to get down to cases comes as no surprise in a project whose gestation, delivery, and struggle to get off the ground are accomplished in a total governmental environment.

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The Editor welcomes letters and comments, particularly pertaining to recently published articles in the Proceedings. A letter should be no longer than 500 words and contain no more than five references. The letter should be signed, and it will be assumed that the letter may be published unless the writer indicates otherwise. The Editor reserves the right to edit letters in accord with Proceedings style and to abridge them if necessary.

Mayo Clin Proc 52:523, 1977

ENT FOR PRIMARY-CARE PHYSICIANS

POSTGRADUATE COURSE
SPONSORED BY MAYO CLINIC-MAYO FOUNDATION

The Department of Otorhinolaryngology of the Mayo Clinic presents its annual program of lectures and discussion on problems of general interest in ear, nose, and throat, including basic guidelines for diagnosis and treatment of diseases of this region. This year the course will be directed to internists, pediatricians, and others who engage in primary-care medicine, as well as to family physicians and general practitioners. This course meets the criteria for credit hours in continuing medical education. The fee for this course is $60.

The course will be held in two identical sessions, on the two Sundays preceding "Clinical Reviews," October 23 and October 30, 1977.

Program

Morning sessions (Lectures)

Welcome
H. Bryan Neel III, M.D.

Is It Menière's Disease?
George W. Facer, M.D.

Hearing Aids in Sensorineural Hearing Loss
Darrell E. Rose, M.D.

Precancerous Conditions in the Upper Airway and Food Passages
Kenneth D. Devine, M.D.

Parotid Swellings
Bruce W. Pearson, M.D.

Understanding Facial Paralysis
George W. Facer, M.D.

Rhinitis
H. Bryan Neel III, M.D.

Afternoon sessions (Case Presentations)

Serous Otitis Media
Stephen G. Harner, M.D.

Ear Pain
Stephen G. Harner, M.D.

Acute Tonsillitis and Peritonsillar Abscess
Thomas J. McDonald, M.D.

Nasal Injury
Thomas J. McDonald, M.D.

Acute Sinusitis
Eugene B. Kern, M.D.

Chronic Sinusitis
Eugene B. Kern, M.D.

For further information, please write: Dr. H. Bryan Neel III, Program Director, Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN 55901.

CLINICAL REVIEWS PROGRAM

Staff members of the Mayo Clinic will present again this year a 3-day program of lectures and discussions on problems of general interest in medicine and surgery. Because the number of physicians who can be accommodated is limited, Clinical Reviews is offered in two identical sessions—October 24, 25, and 26, 1977, and again on October 31 and November 1 and 2, 1977.

The American Academy of Family Physicians and the College of Family Physicians of Canada have approved this program for 23 prescribed hours. As an organization accredited for continuing medical education, the Mayo Clinic-Mayo Foundation certifies that this continuing medical education offering meets the criteria for 23 credit hours in Category I of the Physicians Recognition Award of the American Medical Association. The fee for this course is $100.

The program is as follows:

MONDAY, OCTOBER 24 AND OCTOBER 31

MORNING SESSION

Welcome

Treatment of Diabetic Ketoacidosis Using Low-Dose Insulin

Practical Clinical Points About Aneurysms

Discussion

In-Utero Exposure to Diethylstilbestrol

Diarrhea of Acute Onset—Can the Laboratory Be of Any Help in Its Diagnosis?

Discussion

Implications of Steroid Therapy

Have the Indications for T and A Changed?
Toxemia of Pregnancy

Discussion

Luncheon

AFTERNOON SESSION

How To Avoid Malpractice Problems

Common Skin Malignancies

Update on Hearing Evaluation and Hearing Aids

Discussion

The Surgical Treatment of Hallux-Valgus—What and Why?

Diagnostic Considerations in Unexplained Hypercalcemia

Arthroscopy

Discussion

EVENING SESSION

Panels (Held Simultaneously)

Hormonal Management of Breast Cancer

Carcinoma of the Breast

Subcutaneous Mastectomy—Who Needs It?

Geriatrics in the Nursing Home

Basic ECG Diagnosis

TUESDAY, OCTOBER 25 AND NOVEMBER 1

MORNING SESSION

The Diagnosis and Treatment of Acute and Chronic Asthma

Nutritional Management of the Renal Failure Patient

Discussion

Newer Concepts in Classification and Treatment of Ligamentous Instability of the Knee

Bladder Retraining in Patients With Neurogenic Bladder Dysfunction

Discussion

The Evaluation of GI Bleeding

The Problem of Undescended Testicles

Indications for Computerized Tomography

Discussion

Luncheon—Roundtable Discussions

Puncture Wounds of the Foot

Child and Spouse Abuse Update

Treatment of Strokes

What the Family Physician Should Know About Cosmetic Surgery

Diagnosis and Treatment of Intravascular Coagulation in Bleeding Emergencies

Treatment of Convulsive Disorders

Cardiac Diagnosis by Chest X-Ray

Thyroid Function Tests

Practical Clinical Applications of Echocardiography

Hypertension Management

Early Recognition of Postoperative or Post-traumatic Renal Failure

Office Use of Patient Questionnaires for History Taking

Respiratory Intensive Care

The Child With the Innocent Murmur

"The Hypertension Workup"

AFTERNOON SESSION

The Status of Urine Cytology

Rectal Bleeding in Infants and Children

Medical Treatment of Rheumatoid Arthritis

Discussion

When Does Your Patient Need a TUR?

A Clinician Looks at Sinus X-Rays

Discussion

Treatment of Electrolytes and Blood Gas Problems

An Update on Retinal Surgery

Discussion

EVENING SESSION

Panels (Held Simultaneously)

Recognition and Treatment of Cardiac Dysrhythmias in Acute Myocardial Infarction

Treatment of Infectious Diseases

Psychiatric and Chemical Dependency Problems in Physicians and Their Families

WEDNESDAY, OCTOBER 26 AND NOVEMBER 2

MORNING SESSION

Contact Dermatitis—Recognition and Treatment

What Would You Think if Your Patient Sounded Like This?

Discussion

The Sprained Ankle

Management of the Obese Patient

Discussion

The Sick Sinus Syndrome

What's New and Useful in Hyperlipidemia and Lipoprotein Analysis

Digitalis Toxicity

Discussion

Luncheon—Roundtable Discussions (Same as Tuesday)

AFTERNOON SESSION

Serum Protein Electrophoresis and Immunoelectrophoresis in Clinical Practice

Malaria—The Malignant Mimic: Clinical Considerations

Malaria—The Malignant Mimic: Laboratory Considerations

Discussion

Ultrasound in Obstetrics and Gynecology

Otologic Manifestations of Systemic Disease

The Diagnosis and Management of the Infertile Couple

Discussion

Adjourn

For further information about the program, please write to Mr. William Nietz, Communications, Mayo Clinic, Rochester, MN 55901.

Book Reviews

Pathological Basis of Renal Disease, by M. S. Dunnill, 473 pp, with illus, $35, London: W. B. Saunders Company, 1976

Given the rapid growth of knowledge in renal pathology over the past decade, Dunnill has undertaken a monumental task in presenting historical, experimental, and clinical information in a relatively compact text. Most of the histopathologic information is based on renal biopsy material; there are reasonably complete and up-to-date descriptions and illustrative black and white photomicrographs of light and electron microscopic studies. The illustrations of immunofluorescence are of only fair quality. Current concepts of pathogenesis, especially of the glomerulopathies, are well discussed.

The major emphasis is placed on clinicopathologic correlations, and the chapters, which are generally well organized and very detailed, range widely, dealing with primary glomerulopathies, renal disease associated with systemic diseases and pregnancy, acute tubular necrosis, interstitial nephritis, renal infection, papillary necrosis, and the transplanted kidney. An exception to good organization is the peculiar grouping of bacterial endocarditis, shunt nephritis, and renal complications in narcotic addicts into a single, brief chapter.

Some of the clinical and pathologic material is developed from both old and recent literature and the author tends to combine it, making it difficult to separate the important from the unimportant. Also, there is some adherence to older studies and unduly outmoded statements, such as in the section on diffuse proliferative lupus nephritis: "The prognosis is uniformly bad. Most patients develop irreversible renal failure in two to three years in spite of treatment." More recent studies indicate that most patients with this form of lupus nephropathy improve with treatment.

Another deficit is the author's attempt to summarize an extensive literature on experimental models of nephritis, mechanisms of renal injury, and the etiology of human glomerulonephritis into a brief chapter. Without sufficient background in this area, or an interest in pursuing these subjects by reading many of the experimental papers, one might be discouraged from going further into the book. Dunnill might have prepared his readers better by beginning with a simpler dissertation on the experimental information or, better yet, by starting with the normal anatomy and function of the nephron instead of reserving that information for an appendix.

Although in his preface Dunnill states that he intends the book for the interested general pathologist, physicians, and "clinical students," it may be too detailed for these students of medicine. However, the book would be a useful reference text for the budding renal pathologist and for the nephrologist who is particularly interested in parenchymal renal disease.

James V. Donadio, Jr., M.D.
Division of Nephrology and Internal Medicine

Pain: From Symptom to Treatment, by Manuel M. Villaverde and C. Wright MacMillan, 352 pp, with illus, $22.50, New York: Van Nostrand Reinhold Company, 1977

Villaverde and MacMillan's book stresses the symptomatic treatment of pain and not the diseases causing the pain. The contents of the book are divided into two parts. The first part covers the pharmacology of drugs used to treat pain of various etiologic origins, whereas the second part attempts to specify treatment of pain according to the location of the pain.

In the pharmacologic section of the book, there is a brief discussion of a number of drugs used to suppress or relieve pain. The terse description often does not provide adequate information for prescribing unfamiliar drugs. Also, there are some recent and valuable drugs that have been omitted from various classifications, such as bupivacaine and naloxone.

In the second section of the book, pain is listed according to its anatomic location. For each heading there is a brief description of diseases causing the pain symptom. Headache is the first such symptom, with various categories of diseases following such as systemic infection, circulatory disease, allergies, and local infections. At the end of each specific disease description is a list of the drugs used to suppress the pain symptom. The list often includes acetylsalicylic acid, codeine, and similar drugs.

The book fails to include many of the difficult-to-explain problems of chronic pain and the modalities of treatment presently used for those types of pain. Although some practitioners may find this book useful, it is not recommended for those who are interested in treating diseases or pain problems.

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Department of Anesthesiology

Hemoglobinopathies (Major Problems in Internal Medicine, Volume 12), by H. Franklin Bunn, Bernard G. Forget, and Helen M. Ranney, 316 pp, with illus, $16, Philadelphia: W. B. Saunders Company, 1977

The enormous growth of the literature on hemoglobin poses an extraordinary challenge to those who attempt to review this subject. In the last few decades, the structure, function, genetics, and "molecular biology" of hemoglobin have been elucidated with a minuteness of detail with which the present knowledge of any other protein cannot even remotely be compared. Furthermore, there appears to have been no slackening in the discovery of new hemoglobin variants, now numbering nearly 400 (as compared with "more than 250" when this text was sent to the printer). The authors of *Hemoglobinopathies* have each made many notable contributions to development of our knowledge of hemoglobin. *Hemoglobinopathies* reflects their work and their special areas of expertise. By their design, it is not encyclopedic. No presentation is made of laboratory methods. No guide is provided to the diagnostic evaluation of hemoglobinopathies. The epidemiology of hemoglobinopathies is scarcely touched upon. However, within the scope intended by the authors, they have presented a lucid and thorough exploration of modern concepts of hemoglobinopathies and a well-balanced review of the recent literature, concise enough to be encompassed in fewer than 300 pages (compared with a 1974 text on the same subject of nearly 500 pages), and at a reasonable price. Particularly to be recommended are the chapters on thalassemia, sickle cell anemia, and hemoglobin function. Much has been learned about these aspects of hemoglobin in recent years and these

chapters provide outstanding reviews of this progress. In my judgment, these are among the best accounts of sickling disorders and of thalassemia to have appeared in recent years. Illustrations are numerous, clear, well selected, and well reproduced.

Because *Hemoglobinopathies* surveys a rapidly proliferating literature, it is surprising that imperfections are few. However, it is a reviewer's obligation to note these. In contrast to the authors' statement, hemoglobin E now appears to be the most prevalent rather than the third most prevalent human hemoglobin variant. (The prevalence of hemoglobins E and S may nearly be equal, each being exhibited by about 30 million people.) Because hemoglobin E disorders are virtually limited to the people of Southeast Asia, American physicians rarely encounter this hemoglobin variant. Issue may also be taken with the authors' assertion that hemoglobin E trait is unassociated with hematologic or morphologic abnormalities. In fact, hemoglobin E trait exhibits many features resembling a very mild thalassemia; slight microcytosis is characteristic, and mild erythrocytosis is sometimes encountered. Formerly, the microcytosis was often missed because erythrocyte indices were determined manually and therefore with less precision than by direct measurement of mean corpuscular volume.

An otherwise well-balanced account of unstable hemoglobins surprisingly omits any reference to hemoglobin H disease, which is both an α thalassemia and also by far the most frequently encountered unstable hemoglobin hemolytic anemia. This omission may reflect the authors' geographic perspective, as hemoglobin H disease is most often encountered among the people of Southeast Asia, although it may occur among those of European ancestry and in a mild form it is not uncommon in American blacks. Furthermore, in their tabulation of unstable hemoglobins one encounters inexplicable inclusions (for example, hemoglobin Russ) and omissions (for example, hemoglobin Fort Worth). At least 12 fully characterized unstable hemoglobins are missing from this table.

The authors devote short paragraphs to hemoglobins D Los Angeles, E, Korle-Bu, and I, the last two of which are certainly rare. Paradoxically, they omit altogether a description of hemoglobin G Philadelphia, one of the more frequently encountered hemoglobin variants in North America, one often mistaken by the novice for hemoglobin S, and a variant which has contributed substantially to elucidation of some genetic phenomena.

In a brief paragraph on S/O Arab hemoglobinopathy, the authors err in describing the electrophoretic mobility of hemoglobin O Arab as being like that of hemoglobin S, in agar gel at pH 6.2. In fact, in this medium, hemoglobin O Arab has mobility distinctly cathodal to hemoglobin S, that is, between hemoglobins S and A. The typically sharp band of hemoglobin O Arab in this position renders its identification easy by acid-agar electrophoresis.

The term "congenital Heinz body anemia" ought long ago to have been discarded, because clinically these hemoglobinopathies are infrequently congenital, because Heinz bodies are not characteristic, and because patients who have these hemoglobinopathies commonly are not anemic.

Oversights such as these, inevitable in a new text in a rapidly developing field, detract little from the overall excellence of the authors' presentation. *Hemoglobinopathies* is particularly recommended as a review of hemoglobin function and of the basic mechanisms and clinical features of thalassemias and sickling disorders.

Shortly after submitting the above review, I was asked also to review *Human Hemoglobins* by the same authors, 442 pp, $18 (vs. $16 for the above), same publisher, 1977. I discovered that 265 pages of *Hemoglobinopathies* are included in *Human Hemoglobins*. One of the authors also pointed this out in a letter to me, indicating that these two volumes are oriented to different groups of readers. For the average reader, the additional information contained in *Human Hemoglobins* might be superfluous. Few, if any, would find it worthwhile to buy both books. I would urge interested readers to pay the extra $2 for the more complete treatise. Medical libraries should purchase only *Human Hemoglobins*. A review of this book will follow in a subsequent issue of the *Proceedings*.

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Case Studies in Echocardiography: A Diagnostic Workbook, by Ralph D. Clark, 343 pp, $14.95, Philadelphia: W. B. Saunders Company, 1977

This book is precisely what its title suggests. The authors present selected case histories followed by representative echocardiograms. Each case includes questions and an opportunity for measuring the various parameters of the echogram. Then follows a sketch of the echocardiogram in question, answers to the questions posed, and a discussion and explanation of the findings. This workbook has many excellent features, most especially the format and organization of the data. The opportunity to make measurements and answer questions and compare them to the author's answers is very helpful for the beginner and is a good exercise in self-education. Secondly, the artistic sketches that follow are exceptionally well done and particularly useful for the beginning echocardiographer. Third, the discussion is good and the author emphasizes the areas of echocardiography that require clarification. Finally, the tables that are interspersed, as well as the selected bibliography, are very good.

The limitations of this workbook are, unfortunately, important ones. The major weakness is the quality of the echograms, which in general are only fair. It is unfortunate that the author did not make more and better use of correlative studies—that is, correlation of the echocardiogram with the phonocardiogram, the external carotid trace, the venous pulse trace, and respiration. He also fails to use and emphasize the importance of scanning, both in diagnosis and in identifying valve structures. This is especially true of the tricuspid valve echograms which are presented.

In general, the work is well done. This diagnostic workbook should be helpful to anyone interested in echocardiography and particularly helpful to the novice.

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